SYNTHETIC STUDIES TOWARD PALAU'AMINE AND ENANTIOSELECTIVE TOTAL SYNTHESIS OF BIOGENETICALLY RELATED (+)-PHAKELLIN AND (+)-MONOBROMOPHAKELLIN

A Dissertation

by

SHAOHUI WANG

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

May 2008

Major Subject: Chemistry

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Approved by:

Chair of Committee,	Daniel Romo
Committee Members,	Kevin Burgess
	Thomas D. McKnight
	Daniel A. Singleton
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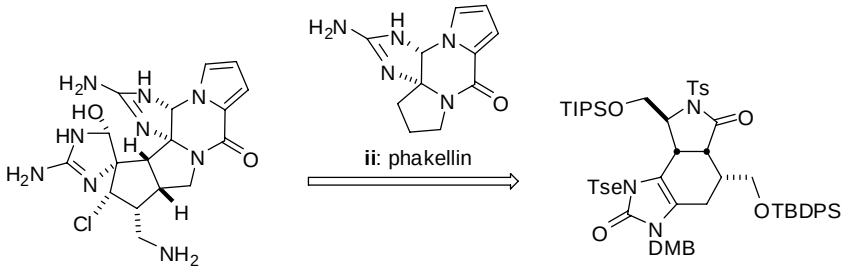
ABSTRACT

Synthetic Studies toward Palau'amine and Enantioselective Total Synthesis of Biogenetically Related (+)-Phakellin and (+)-Monobromophakellin. (May 2008)

Shaohui Wang, B.S., Peking University, China

Chair of Advisory Committee: Dr. Daniel Romo

Oroidin alkaloids, also known as pyrrole-imidazole alkaloids, have become a hot area of chemical and biological research due to their diverse and intriguing structural features and biological activities. Palau'amine (**i**), one of the hexacyclic oroidin-derived secondary metabolites, contains a fully substituted chloro-cyclopentane ring, a piperazinone moiety and two cyclic guanidines. With the uniqueness and complexity of its structure, palau'amine has been a synthetic challenge and has not yet succumbed to total synthesis. The overall objective of this work was to explore synthetic pathways toward palau'amine and biogenetically related congeners.

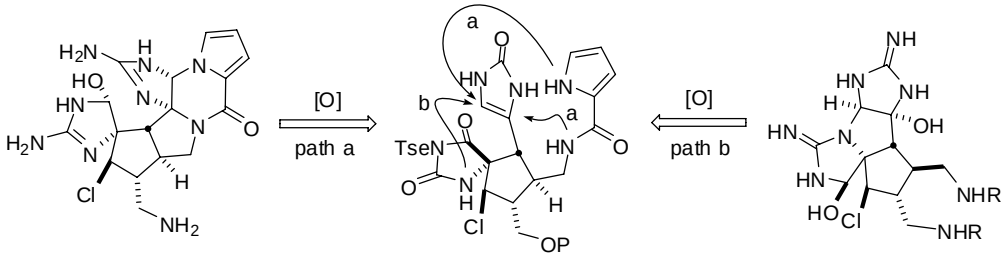


i: palau'amine originally assigned structure

ii: phakellin

iii: Diels-Alder adduct

Most of the work was focused on developing a synthetic pathway for the palau'amine structure proposed in its isolation report dated back to 1993. Starting from a Diels-Alder adduct (**iii**), oxidation/chlorination followed by phakellin (**ii**) annulation afforded an advanced pentacyclic intermediate possessing all the carbon framework and all but one ring system of palau'amine. Recently, however, a series of reports questioned the originally proposed palau'amine structure and called for a revision of the stereochemistry of two carbon centers (**iv**). Now palau'amine has an identical chlorocyclopentane core with axinellamine (**vi**). With the target changed, we devised a new biomimetic pathway toward both natural products via a common intermediate (**v**), which was synthesized in 12 steps from the Diels-Alder adduct (**iii**).



iv: palau'amine revised structure

v: common intermediate

vi: axinellamine A

DEDICATION

To my parents, Changxi Wang and Qiumei Zhang

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my committee chair, Dr. Daniel Romo, for his guidance and support over the past five years on this challenging research project. I am forever grateful for him providing me the opportunity to study and improve in this exciting field. I also want to thank my committee members: Dr. Kevin Burgess, Dr. Thomas D. McKnight and Dr. Daniel A. Singleton for their support throughout the course of this work.

Thanks also go to my friends and colleagues in the Romo research group, both the previous and current members. Without you, it would have been impossible to accomplish what I have done in the group. Specially, I would like to extend my gratitude to Dr. Anja S. Dilley and Dr. Paul J. Dransfield. You guys helped me through my early years on this project and I really appreciate that. I am thankful to my labmates, Vikram Purohit and Francisco M. Franco-Torres, for the discussions and laughs in the lab, chemistry related or not. And I am grateful to all my good friends I met in Davis and College Station: Chris and Michelle, Zheng, Andrea, Junyan and Shan, Qingsong and Jing, Liang and Han, Wei, Gang, Yu and Scott …

Last but not lease, my love and thanks go to my family: my parents, Changxi Wang and Qiumei Zhang, my brother, Shaofeng Wang, and my wife, Juan Yang. Thank you very much for your unconditional love and support. I am sorry that we have to be separated for a while, but I always think of you everyday.

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CHAPTER I

AN INTRODUCTION TO PALAU'AMINE AND RELATED OROIDIN-DERIVED MARINE ALKALOIDS: HISTORY AND RECENT DEVELOPMENTS

A. Introduction

Since the beginning of recorded history, Mother Nature not only provides human being's material desire, but also serves as a source of remedies and cures for human illness. Natural herbs and plants have been used by Asian people since ancient times to treat many kinds of diseases and to maintain health. It is known that more than 80% of drugs used in traditional Chinese medicine (TCM) come from plants found in China mainland.[1] Western medicines also take advantage of natural products extracted from plants as the major components of many pharmaceuticals. As a matter of fact, about 75% of anti-HIV drugs, 62% of anti-cancer drugs and roughly 52% of all drugs currently used are either derived directly from natural products or derived from natural product leads.[2] While terrestrial plants provide numerous natural products with medicinal properties, marine organisms living in oceans, are another incredibly rich source of bioactive natural products.

Marine organisms, such as sponges, tunicates, algae, coelenterates, mollusks and microorganisms etc.,[3] produce a broad range of structurally diverse and extremely

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This dissertation follows the style of *Journal of the American Chemical Society*.

bioactive compounds that demonstrate potent anti-tumor, anti-inflammatory, anti-viral, analgesic and immunosuppressive activities.[4] Large numbers of new marine natural products are discovered each year. With their intriguing structures and often potent biological activities, many of these compounds have attracted chemists and biologists to pursue their total synthesis and evaluate the potential pharmaceutical applications of these natural products and their structural derivatives.[5] There are many reasons to pursue a total synthesis, such as making large quantity of a certain natural product due to its limited accessibility from nature, making structurally diverse derivatives to study their biological activities, and discovering new organic reactions and synthetic methodology to advance the science of organic synthesis.

Among all those marine natural products there is one family of polycyclic alkaloids isolated from different species of marine sponge, i.e. *Agelas, Hymeniacidon, Axinella, Acanthella, Cymbastella, Phakellia*, known as pyrrole-imidazole alkaloids.[6] This family of fascinating alkaloids has a total of about 100 known members,[7] and they are biogenetically related via a common key biosynthetic precursors, oroidin (**1.1**), composed of 3-amino-1-(2-aminoimidazolyl)prop-1-ene (AAPE, **1.2**) and pyrrole (or dibromopyrrole) carboxylic acid (**1.3**) (Figure 1).[8]

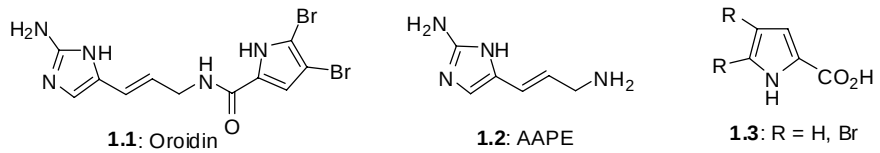


Figure 1. Oroidin (**1.1**), the key to the pyrrole-imidazole alkaloids

B. Isolation and Biological Activity

The pyrrole-imidazole alkaloids include an array of structurally diverse and complex secondary metabolites, which often have some interesting bioactivities. Palau'amines (**1.4**-**1.6**), axinellamines (**1.7**, **1.8**) and massadine (**1.15**) represent the complexity of the oroidin family of marine alkaloids (Figure 2). New members of pyrrole-imidazole alkaloids with unprecedented structural features are constantly being discovered in the course of searching for novel chemical entities with potential beneficial biological activities from oceanic organisms (*vide infra*).

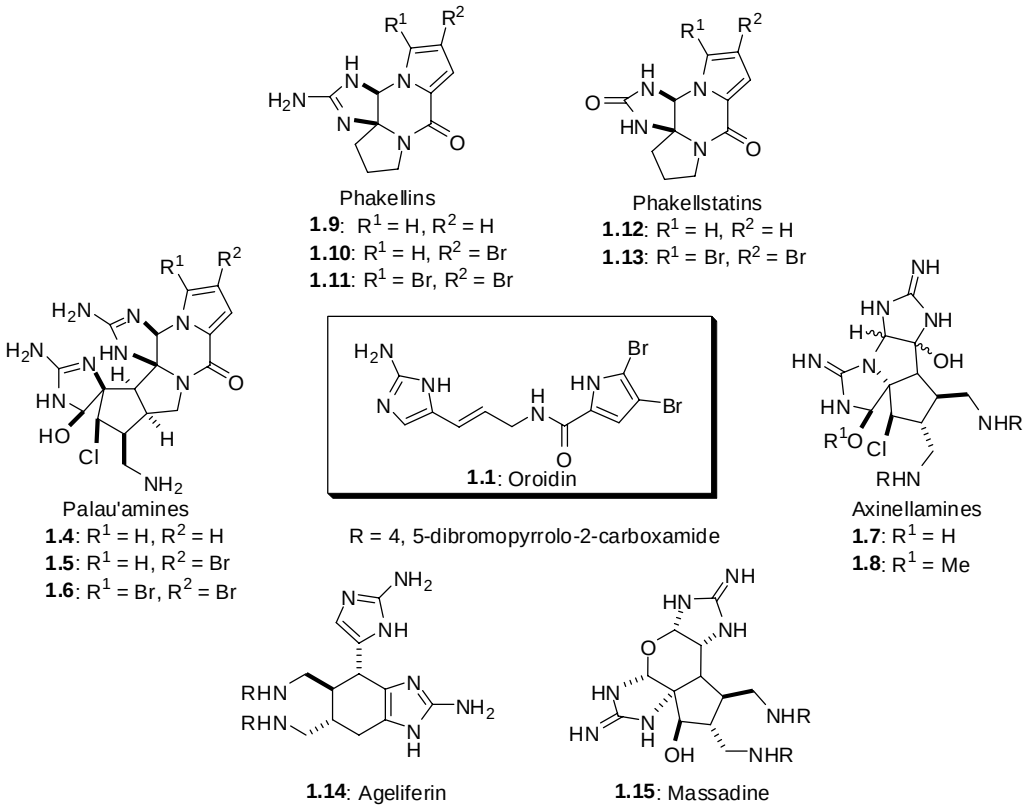


Figure 2. Representative members of oroidin-derived alkaloids

1. Palau'amines and Styloguanidines

Palau'amine (**1.4**) was first isolated in 1993 by Kinnel and Scheuer from the Belau sponge *Stylotella aurantium* obtained from Western Caroline Islands.[9] Also isolated along with palau'amine were its monobrominated (**1.5**) and dibrominated (**1.6**) analogs (Figure 3). Palau'amine exhibits potent cytotoxicity against tumor cell lines P-388 (IC_{50}: 0.1 μg/ml), A549 (0.2 μg/mL), HT-29 (2 μg/mL), and KB (10 μg/mL), antibiotic activities, antifungal activities, and shows particularly potent immunosuppressive activity (IC_{50}<42.8nM) as determined by mixed lymphocyte reaction.[10]

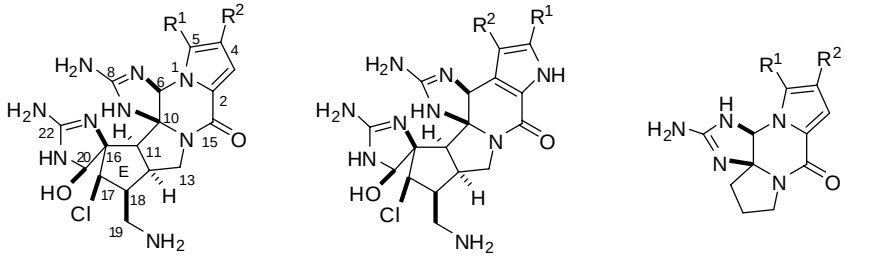


Figure 3. Palau'amines and structurally related natural products

The structure of palau'amine was elucidated by extensive NMR analysis and chemical derivatization, but its absolute stereochemistry has not been determined unambiguously. The assigned structure was based on the similarity of the circular dichroism spectra of palau'amine and monobromophakellin hydrochloride (**1.10**), whose absolute stereochemistry was determined by X-ray crystallographic analysis of

monoacetyldibromophakellin.[11] Palau'amine is stable in weakly acidic conditions, but decomposes rapidly when the pH is over 6.5. Its instability and complex hexacylic and highly nitrogeneous structure make palau'amine a daunting target for total synthesis.[12] Much of the structural complexity of palau'amine resides in the central cyclopentane ring (E ring, Figure 3), which has five contiguous stereocenters, and each of the carbons is substituted on the concave α face. In addition, the two spirocyclic guanidine substructures also present challenges to synthesis. Another interesting structural feature is that palau'amine contains a phakellin subunit, which links the two natural products together biosynthetically and also when one considers the total syntheses of these alkaloids.

The structural isomers of the palau'amines, the styloguanidines (**1.16**-**1.18**, Figure 3), were isolated from the same sponge species (*Stylotella aurantium* obtained from the Yap Sea) by Kato and co-workers in 1995.[13] In their 1998 report,[10] Kinnel and Scheuer also mentioned that all the three styloguanidine analogues were present in the sponge they analyzed previously. Styloguanidine shows strong chitinase inhibiting ability against *Schwanella sp.* (2.5 μg/disk, assayed by the squid chitin agar plate method).

2. Axinellamines

Axinellamines are another series of natural products derived from oroidin. What links axinellamines and palau'amines together is the cyclopentane core. Both oroidin-dimeric derivatives have a cyclopentane moiety that is substituted with similar functional

groups, but with different stereochemistry. In 1999, axinellamines were isolated by Quinn and coworkers from the sponge *Axinella sp.* collected off the coast of Australia.[14] The structures were elucidated by extensive 1D and 2D NMR analysis, but the absolute stereochemistry was not known (Figure 4). Only axinellamines B-D were reported to have weak antibacterial activity (1000 μg/mL) against *Helicobacter pylori*, a bacterium associated with pepticular and gastric cancer.

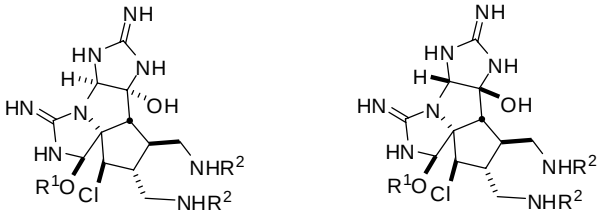


Figure 4. Structures of axinellamines

3. Phakellins and Phakellstatins

The phakellins (**1.9-1.11**, Figure 2) also belong to the pyrrole-imidazole family of marine alkaloids and are proposed to be derived biosynthetically from oroidin (**1.1**) and congeners.[7] The monomeric oroidin derivative (-)-dibromophakellin (**1.11**) and (-)-monobromophakellin (**1.10**) were initially isolated by Sharma and Burkholder in 1969[15] from the marine sponge *Phakellia flabellata* and subsequently, the enantiomeric (+)-dibromophakellin (*ent*-**1.11**) was isolated by Ahond, Poupat and co-workers from *Pseudoaxinyssa cantharella* in 1985.[16] Since the initial isolation report, (-)-

dibromophakellin (**1.11**) has also been isolated from other different sponge species.[17,18] Phakellin (**1.9**) has not been isolated from a natural source, but was obtained by hydrogenolysis of dibromophakellin (**1.11**).[15] The structures of dibromophakellin and monobromophakellin were determined by analysis of NMR and other spectroscopic data, and were confirmed by X-ray crystallography data of monoacetyl (-)-dibromophakellin. Dibromophakellin shows mild antibacterial activity against *Bacillus subtilis* and *Escherichia coli*, as well as antitumor activities (Table 1).

The phakellstatins (**1.12**, **1.13**) are related members of this family bearing a cyclic urea rather than a cyclic guanidine (Figure 2). The isolation of (-)-dibromophakellstatin (**1.13**) was reported in 1997 by Pettit and co-workers.[18] The alkaloid was isolated from *Phakellia mauritiana* through a bioassay-guided isolation procedure using human tumor cell lines (Table 1), and displayed far more potent antitumor activities than dibromophakellin. The structure and absolute stereochemistry of (-)-dibromophakellstatin (**1.13**) was determined by spectroscopic data and X-ray crystallography analysis. The presence of bromine heavy atoms helped the determination of absolute stereochemistry by pronounced anomalous dispersion effects.

Table 1. Cell growth inhibitory activity of dibromophakellin and dibromophakellstatin

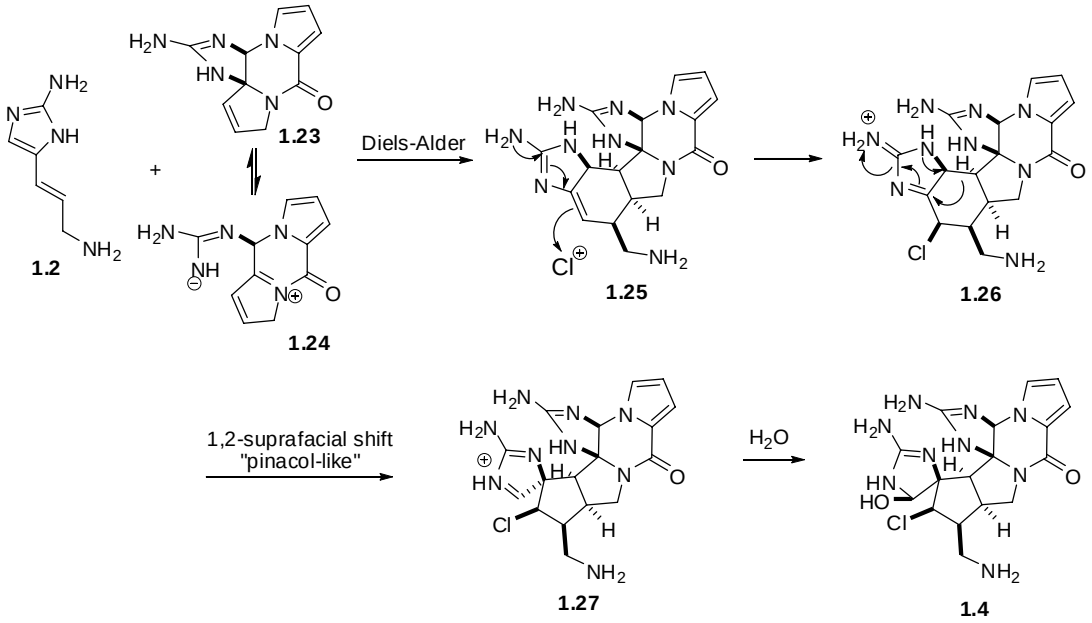
Human cancer cell lines	ED_{50} (μ g/mL)	
	Dibromophakellin	Dibromophakellstatin
ovary (OVCAR-3)	15.7	0.46
brain (SF-395)	18.8	1.5
kidney (A498)	17.8	0.21
lung (H460)	22.0	0.62
colon (KM20L2)	20.1	0.11
melanoma (SK-MEL-5)	17.0	0.11

C. Biosynthetic Pathways

Kinnel and Scheuer proposed that palau'amine orginates from a Diels-Alder reaction between dehydrophakellin (**1.23**) and a truncated oroidin (AAPE, **1.2**).[10] Subsequently, a presumed chloroperoxidase-mediated chlorination initiates a 1,2-shift /ring contraction sequence to deliver the palau'amine structure (Scheme 1), a process with some precedent.[19] In this initial proposal, the idea that dehydrophakellin (**1.23**) could serve as a dienophile in the Diels-Alder reaction was unsettling as its reactivity would be expected to be low in this regard. However, the ring-opened form of dehydrophakellin featuring an allylic acyliminium species (**1.24**), which may indeed be formed in an enzyme active site, would be a highly reactive denophile due to the strong electron withdrawing acyliminium functionality. Thus, Romo and co-workers proposed a refinement to the Kinnel/Scheuer biosynthetic pathway that proceeds through the ring-opened acyliminium species **1.24** leading to Diels-Alder adduct **1.25**. Subsequent chlorination initiates the 1,2-pinacol-like shift/ring contraction cascade leading to the

cyclopentane bearing the iminium species **1.27**, which is then trapped with water to deliver palau'amine (**1.4**).[20]

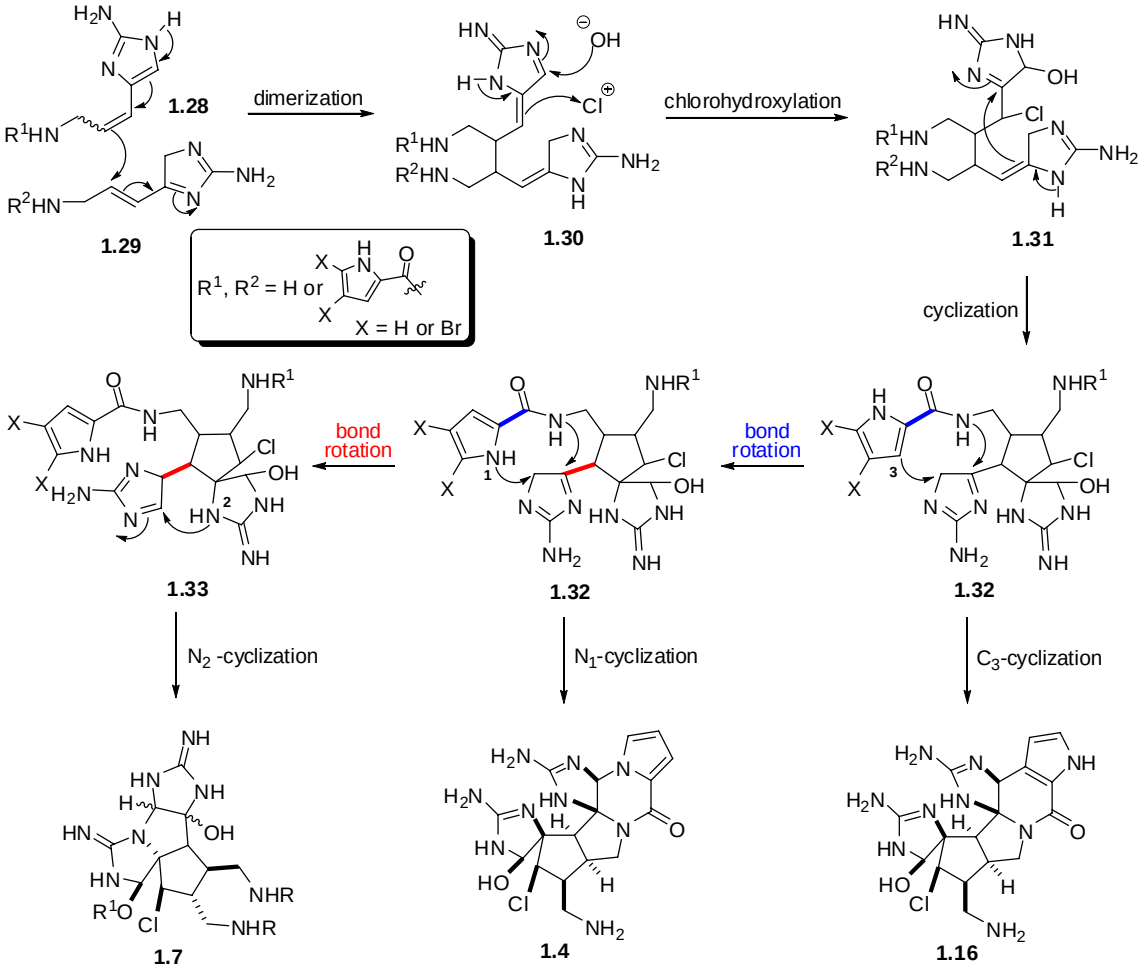
Scheme 1



With the discovery of a variety of structurally related oroidin-derived marine alkaloids, Al-Mourabit and Potier proposed universal chemical pathways towards numerous pyrrole-imidazole alkaloids of this family, based on the tautomerism and ambivalent reactivity of 2-aminoimidazole precursors.[8] These chemical pathways provided helpful information and directions for biosynthetic investigations. According to their proposal, palau'amine and its congeners originate from a dimerization of oroidin tautomers **1.28** and **1.29** (Scheme 2). Chlorohydroxylation and subsequent cyclization give the chloro-cyclopentane structure **1.32**. This intermediate then undergoes oxidation

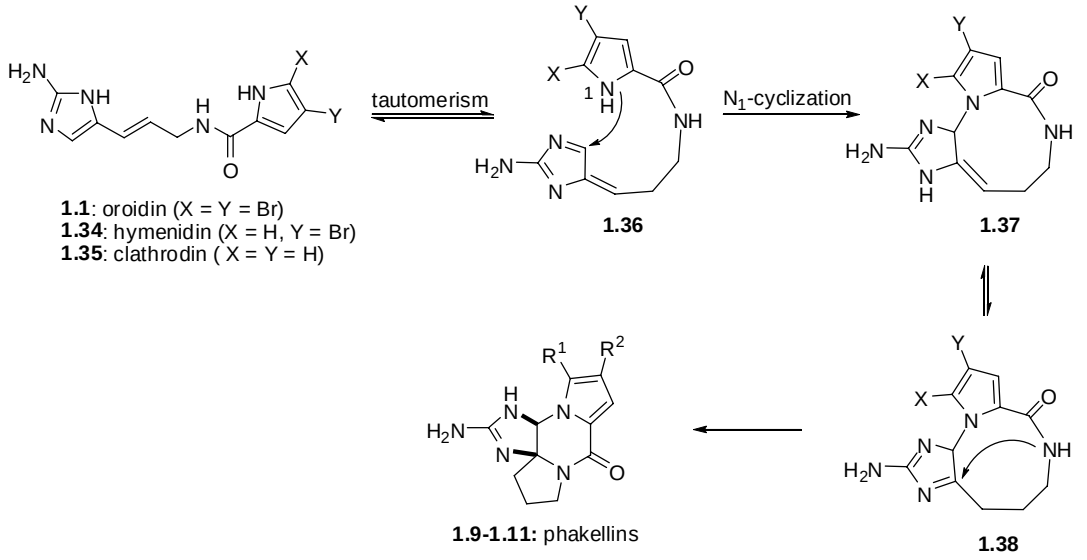
and different modes of intramolecular cyclization to form styloguanidines (C3-cyclization), palau'amines (N1-cyclization) and axinellamines (N2-cyclization).

Scheme 2



Phakellins (**1.9**-**1.11**), one class of monomeric oroidin derivatives, can be generated from intramolecular cyclization of linear oroidin and congeners (hymenidin **1.34** and clathrodin **1.35**), as depicted by Al-Mourabit and Potier (Scheme 3).[8]

Scheme 3

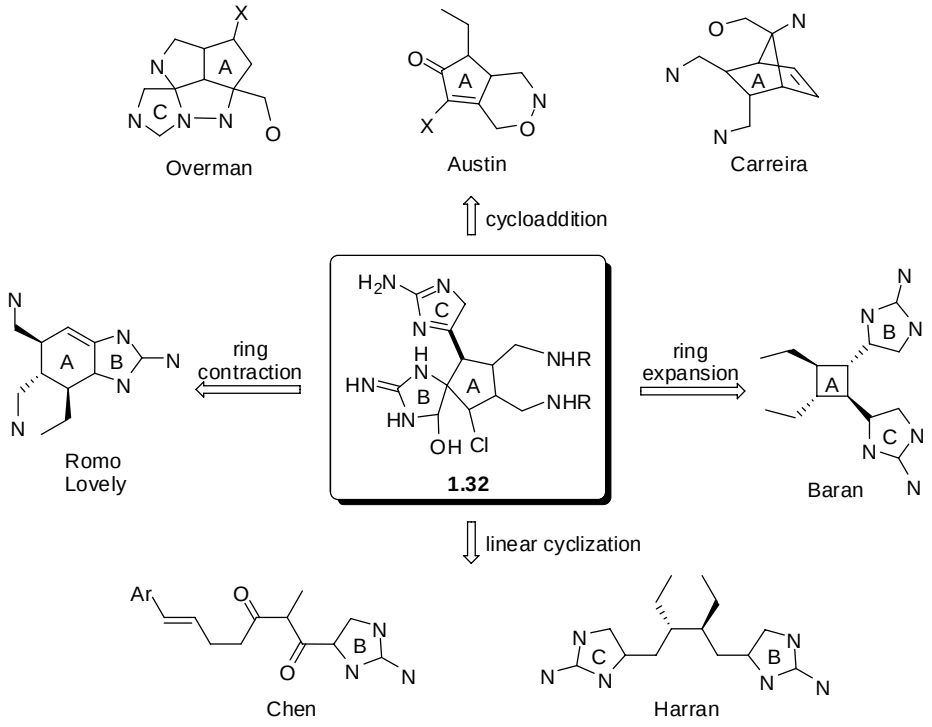


D. Previous Synthetic Studies

Since the reports of the isolation of palau'amines, styloguanidines and axinellamines, many research groups took on the synthetic challenges this class of molecules present and reported their diverse approaches towards these hexacyclic marine alkaloids.[7,12] The synthetic strategies towards the chloro-cyclopentane core structure **1.32**, the proposed biosynthetic precursor of palau'amines, styloguanidines and axinellamines, can be classified into four distinctive groups (Scheme 4). Overman,[21] Austin[22] and Carreira[23] use a cycloaddition strategy to construct the cyclopentane (A ring). Romo[20, 24] and Lovely[25] apply a ring contraction strategy on the cyclohexene intermediate obtained from Diels-Alder reactions. Baran's[26] strategy includes a ring

expansion of a cyclobutane structure to cyclopentane. Chen[27] and Harran[28] take advantage of linear oxidative cyclization to build the cyclopentane ring system.

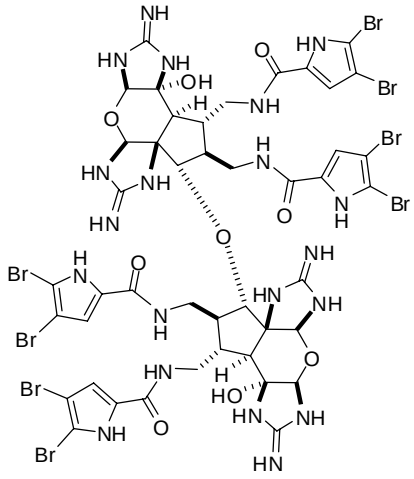
Scheme 4



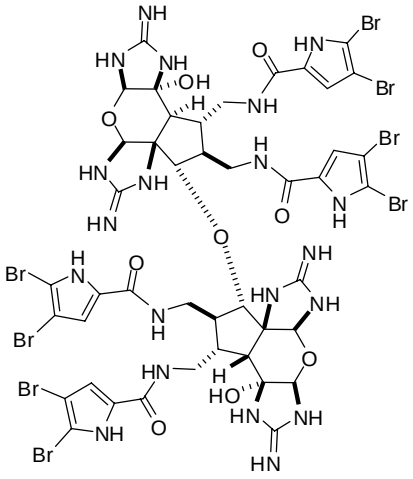
E. New Isolates and Recent Structural Revision of Palau'amine

There are about 100 known pyrrole-imidazole alkaloids reported in literature.[7] Almost all of these secondary metabolites are the monomeric or dimeric derivatives of oroidin (**1.1**) and congeners (**1.34**, **1.35**). So far, the ultimate complexity of pyrrole-imidazole alkaloids is presented in the molecules of stylissadine A and B (**1.39** and **1.40**, Figure 5). Köck[29] and Quinn[30] discovered these two tetrameric oroidin-derivatives independently at the same time. Stylissadine A and B were isolated from the Caribbean

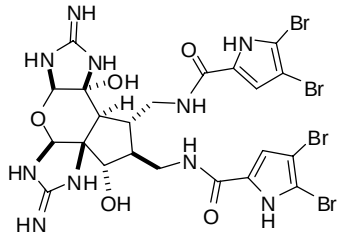
sponge *Stylissa caribica* by Köck and from the Australian sponge *Stylissa flabellata* by Quinn, respectively. As the largest and most complex oroidin alkaloids, stylissadines were major challenges in terms of structural elucidation. Stylissadines have some minor activities against several pathogenic bacteria, fungi, and cultures of mice fibroblasts.[29] Most significantly, according to Quinn's report,[30] stylissadine A and B are antagonists of the $P2X_7$ receptor, an important inflammatory target, having IC_{50} values of 0.7 μM and 1.8 μM respectively.



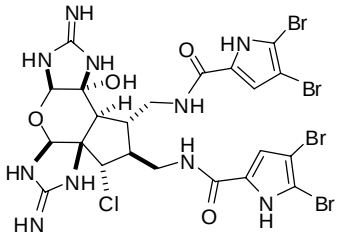
1.39: stylissadine A



1.40: stylissadine B



1.15: massadine



1.41: massadine chloride

Figure 5. Massadine, massadine chloride and stylissadines

Stylissadines are the dimers of a known oroidin-alkaloid massadine (**1.15**), which was isolated from marine sponge *Stylissa* aff. *massa* by Fusetani and coworkers.[31] Massadine chloride (**1.41**, Figure 5), which possesses the common chloro-cyclopentane core moiety found in many other dimeric oroidin-alkaloids such as palau'amines, styloguanidines and axinellamines, is thought to be the biosynthetic precursor of both massadine and stylissadines (*vide infra*, Chapter III). Recently, the isolation of massadine chloride from the Caribbean marine sponge *Stylissa caribica* by Köck and Baran provides sound ground for this speculation.[32]

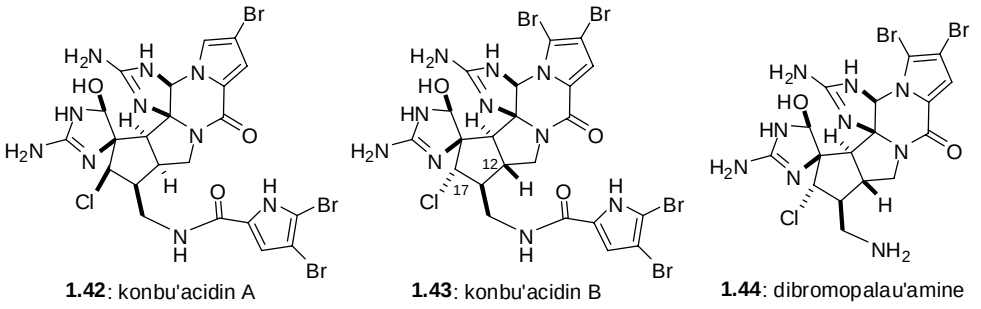


Figure 6. Konbu'acidin B and revised structure of dibromopalau'amine

Isolated together with stylissadines from the Australian sponge *Stylissa flabellata* were konbu'acidin B (**1.43**) and dibromopalau'amine (**1.44**).[30] Advanced NMR techniques and close examination of ROSEY and proton coupling constant data allowed the assignment of the structure as shown in Figure 6. The structure of konbu'acidin B was determined to be quite different from the known konbu'acidin A,[33] in terms of the hexacyclic main skeleton. The stereochemistry of C12 and C17 centers were proved to

be opposite to what was proposed previously. Dibromopalau'amine also had the same structural discrepancy with the previously accepted structure, suggesting some possible misassignments in the original isolation report.[9,10]

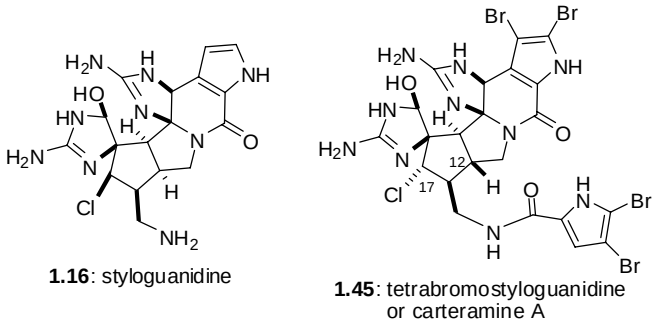


Figure 7. Structure of tetrabromostyloguanidine/carteramine A

The questions over the structural assignment of palau'amine and congeners were cleared when Köck reported isolation and structural elucidation of tetrabromo-styloguanidine (**1.45**, Figure 7).[34] Based on convincing evidence from 1D, 2D-NMR data and advanced computational analysis, the hexacyclic skeleton of tetrabromostylo-guanidine was determined to be different from the previously accepted structure of styloguanidine, with the C17 and C12 stereochemistry being revised. Another independent report on the isolation of the same natural product from the marine sponge *Stylissa carteri* by Matsunaga and co-workers also pointed to the same structural revision.[35] Tetrabromostyloguanidine was named carteramine A in their report, and was found to inhibits the chemotaxis of neutrophils (IC_{50} = 5 μM). To directly confirm the necessity of a structural revision for palau'amine, Quinn and co-workers isolated

palau'amine from the sponge *Stylissa flabellata*, the same marine sponge from which they isolated stylissadine A and B, and based on detailed analysis of 2D ROESY and 1D NOESY data, they concluded that the original structural assignment was incorrect.[36]

In summary, the structure of palau'amine was revised based on recent independent findings from three research groups. The revised structure (**1.46**, Figure 8) has the opposite stereochemistry on the C12 and C17 centers compared to the originally proposed structure (**1.4**), however the absolute stereochemistry of palau'amine is still not known. The most notable feature of the revised structure is a highly strained *trans*-fused azabicyclo[3.3.0]octane moiety. The original proposed *cis*-fused 5,5-bicycle is less strained by approximately 27.3 kJ/mol (6.52 kcal/mol). According to a literature survey, only 10 out of over 2000 bicyclo[3.3.0]octane structure fragments have *trans*-fused junctions.[37] With the revised structures of many related oroidin alkaloids, a refined and more convergent biosynthetic pathway was laid out by Köck and Baran,[37] based on the original biosynthesis proposal by Al-Mourabit and Potier.[8]

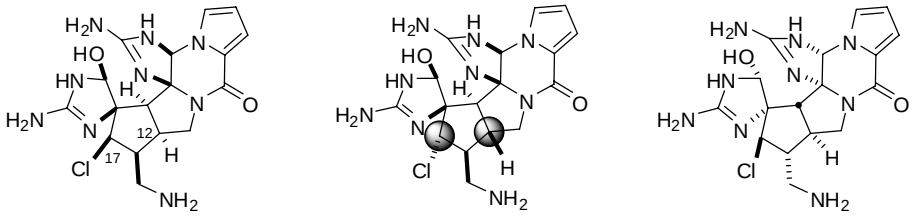
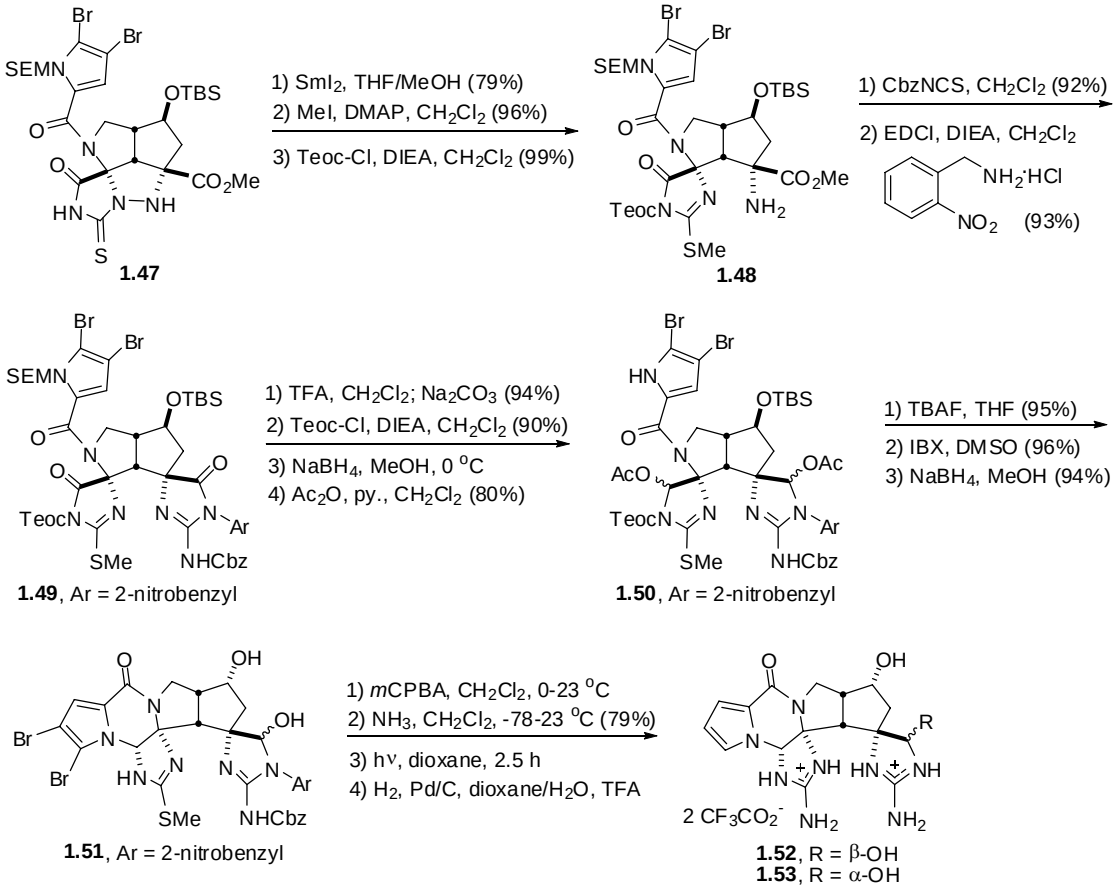


Figure 8. Structure revision of palau'amine

Overman's recent work on the synthesis of palau'amine analogues also provides some strong evidence for the misassignment of palau'amine structure reported 14 years ago. Hexacyclic palau'amine analogues **1.52** and **1.53** (Scheme 5), which possess the two cyclic guanidine functional groups and the *cis*-fused azabicyclo[3.3.0]octane core, were synthesized in 16 steps from cycloadduct **1.47**.[38] Access to these analogues allows the first direct comparison of their NMR data with the data of natural palau'amine. This comparison provides convincing evidence supporting the revised trans configuration of the azabicyclo[3.3.0]octane ring system of palau'amine and congeners.

Scheme 5



F. Conclusion

Natural products, regardless of their isolation sources, can exhibit a large array of biological activities. In conjugation with their diverse and novel structural features, they have become an important sector in scientific research, studied in search for potential therapeutic agents, applied as probes for understanding biomechanistic pathways, pursued in the efforts of discovering novel chemical transformations, or targeted as pure synthetic challenges. Oroidin-derived marine alkaloids, also known as pyrrole-imidazole alkaloids, with their complex and challenging structures and potent bioactivities, are receiving increasing attentions from not only chemists but also chemical biologists.

CHAPTER II

DEVELOPMENT OF A NOVEL ELECTRONICALLY ADJUSTABLE NITROGEN PROTECTING GROUP -- TOSYLVINYL (TSV) AND ITS APPLICATION IN PALAU'AMINE/AXINELLAMINE SYNTHESIS*

A. Background

Our initial approach towards palau'amine and related pyrrole-imidazole alkaloids was inspired by Kinnel and Scheuer's biosynthetic proposal (Chapter I, Scheme 1) for palau'amine. A viable and rapid synthetic pathway was envisioned to assemble the spirocyclic core structure of axinellamines and related bisguanidine alkaloids, via a Diels-Alder reaction, oxidation, chlorination/1,2-shift sequence (Scheme 6). The diene (**2.4**) for the Diels-Alder reaction comes from DL-tartaric acid (**2.7**) and urea (**2.6**), and the dienophile (**2.3**) comes from the more readily available natural L-pyroglutamic acid (**2.5**),[39] even though the originally proposed stereochemistry of palau'amine would require the use of D-pyroglutamic acid. Once the synthesis of palau'amine (*ent*-**1.4**) is accomplished and its absolute stereochemistry is validated, the total synthesis can be carried out in an enantiomeric fashion to give either enantiomer.

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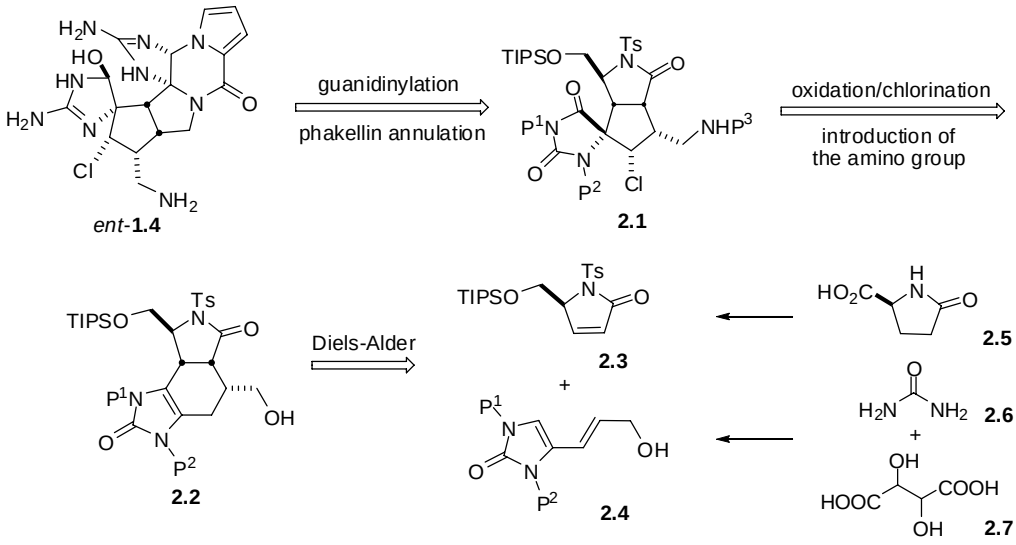
* Reproduced in part, with permission, from "Highly Regioselective Diels-Alder Reactions toward Oroidin Alkaloids: Use of a Tosylvinyl Moiety as a Nitrogen Masking Group with Adjustable Electronics", P. J. Dransfield, S. Wang, A. Dilley and D. Romo, *Org. Lett.* **2005**, *7*, 1679-1682; copyright 2005, by American Chemical Society.

Scheme 6



Regarding the Diels-Alder reaction, the first key step in our synthesis, there are some selectivity issues to be considered. The endo products are expected, as in reported cycloaddition reactions for related dienophiles.[40] As for facial selectivity, the diene should approach the dienophile from the less sterically hindered face (Figure 9). The regioselectivity of the Diels-Alder reaction can be controlled by the two protecting groups on the imidazolone ring of the diene. We reasoned that use of a strongly electron withdrawing group (Ewg) on N1 and an electron donating group (Edg) on N2 would perturb the orbital coefficients of the diene and lead to high regioselectivity (Figure 9). Indeed, when benzyl protecting groups were used for both nitrogens in the diene imidazolone ring, only moderate regioselectivity was observed, yielding two regioisomeric Diels-Alder adducts **2.9** and **2.10** (Scheme 7). Changing the protecting group of N1 from benzyl to tosyl, a strong electron-withdrawing group, and the

protecting group of N2 from benzyl to 3,4-dimethoxy benzyl, a more electron-rich group, did give exclusively only the desired regioisomer **2.12** (Scheme 7).[39]

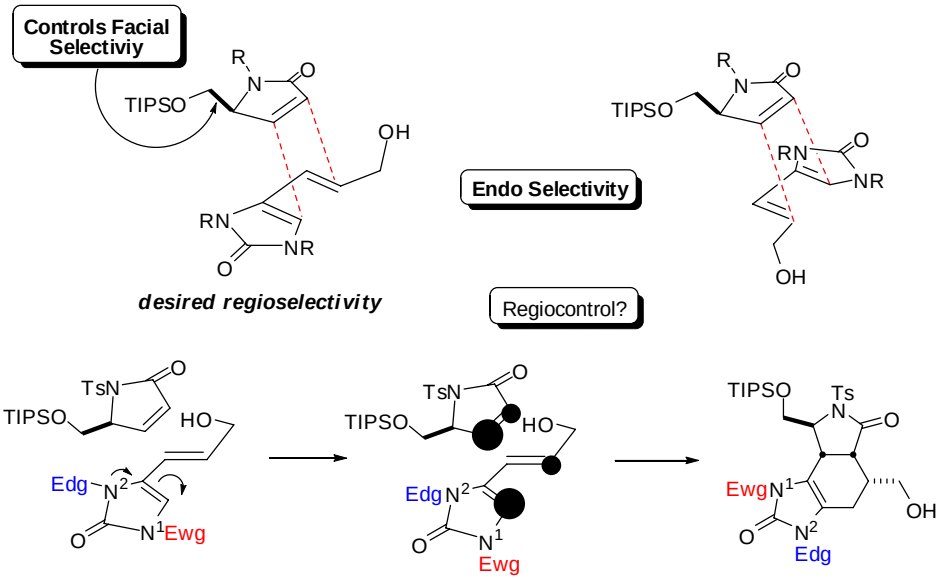
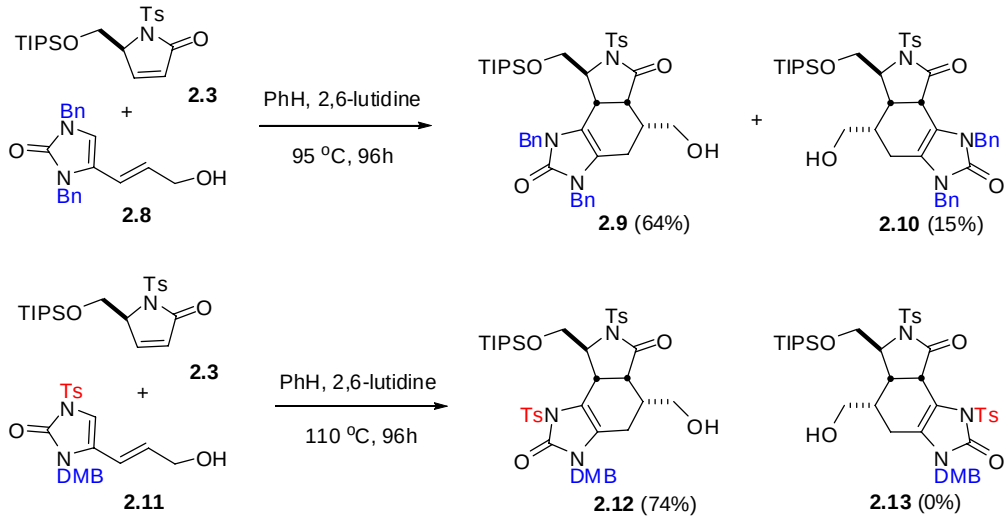


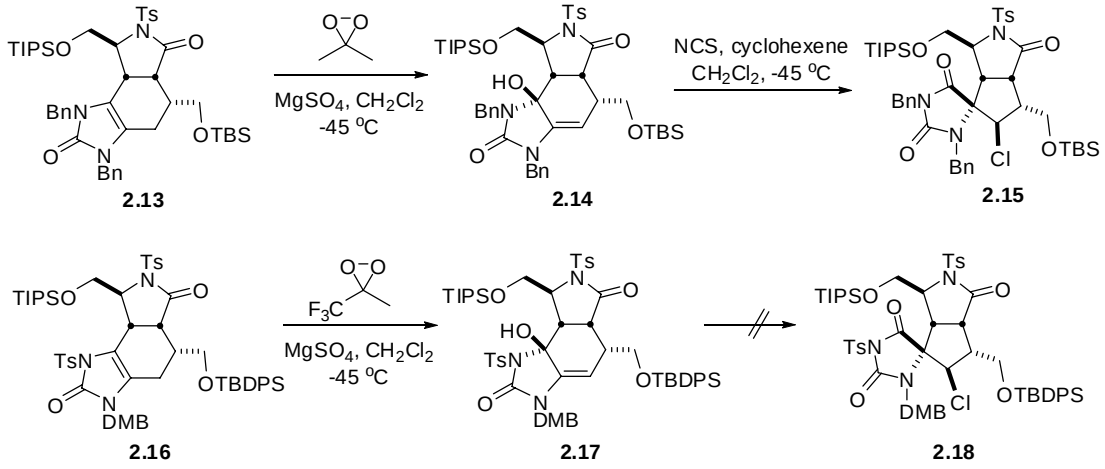
Figure 9. Selectivity issues in the Diels-Alder reaction

Scheme 7



Thus, the tosyl group at N1 had indeed provided the electronics for a highly regioselective Diels-Alder process. Subsequent oxidation of the TBDPS-protected Diels-Alder adduct **2.16** to allylic alcohol **2.17** in this case required the use of trifluorodimethyl dioxirane[41] presumably due to the the tosyl group that rendered the olefin less nucleophilic (Scheme 8). Previously, oxidation of the TBS-protected dibenzylated adduct **2.13** could be achieved in near quantitative yield with dimethyl dioxirane[42] and the subsequent chlorination went smoothly with NCS to give the chlorocyclopentane **2.15**.[24a] However, attempts to effect the subsequent chlorination on the Ts-protected allylic alcohol **2.17** were unsuccessful using a range of chlorinating reagents including NCS, chloramine-T, sodium hypochlorite, 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one, and chlorine gas.[39]

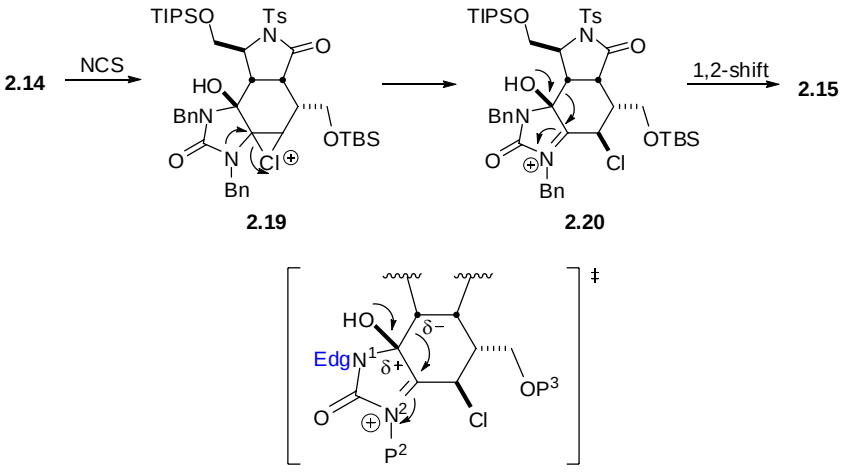
Scheme 8



B. Design of an Electronically Switchable Protecting Group

These observations indicate that an electron-withdrawing protecting group (such as Ts) on N1 clearly benefits the regiochemical outcome of the Diels-Alder reaction, however the subsequent chlorination/1,2-shift cascade requires an electron-rich protecting group on N1, presumably to stabilize the partial positive charge developed on the tertiary *N,O*-hemiaminal carbon in the transition state of the pinacol-type rearrangement (Scheme 9).

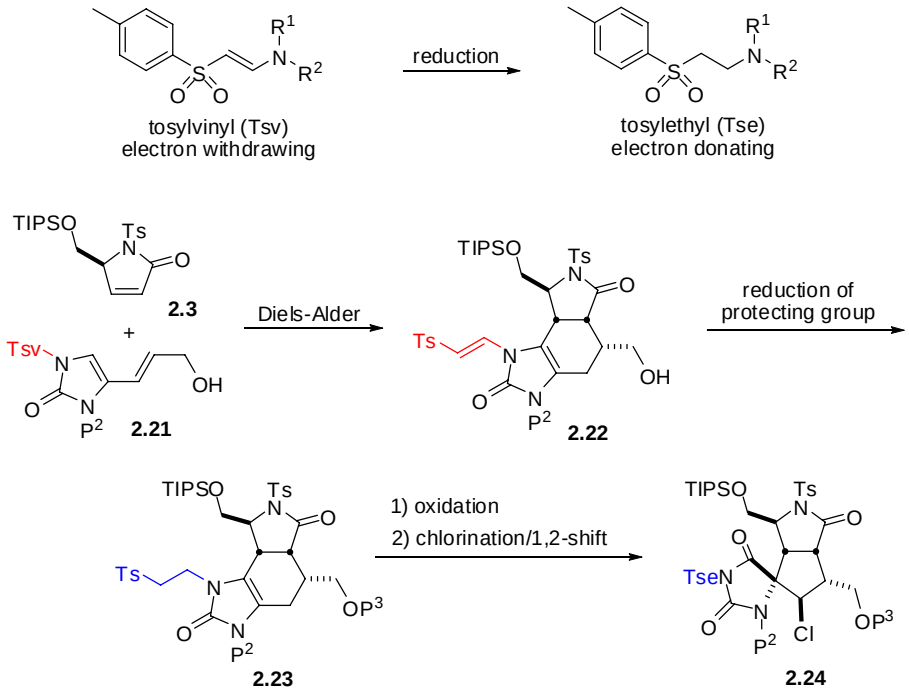
Scheme 9



Generally, this situation would require a protecting group switch. To circumvent this problem, we devised an electronically switchable protecting group which can serve as an electron withdrawing group (Ewg) in the Diels-Alder reaction and then can be reduced to an electron donating group (Edg) to fulfill the electronic requirement in the following rearrangement step. In this regard, we envisaged the use of a tosylvinyl (Tsv)

group[43] (a vinylogous tosyl group), to approximate the electron-withdrawing nature of a tosyl group that is necessary for a regioselective Diels-Alder reaction (Scheme 10). Subsequent olefin reduction would generate a tosylethyl (Tse) protecting group[44] that will serve as a more el ectron rich group determined to be necessary for the chlorination/ring contraction sequence.

Scheme 10



The utility of protecting groups in organic synthesis for controlling chemoselectivity continues to drive advances in this area. The recent development of the *p*-nitrobenzenesulfonyl (nosyl) group by Fukuyama for nitrogen alkylation via Mitsunobu processes nicely illustrates an exciting new direction towards the development of protecting groups that, in addition to functional group masking, serve

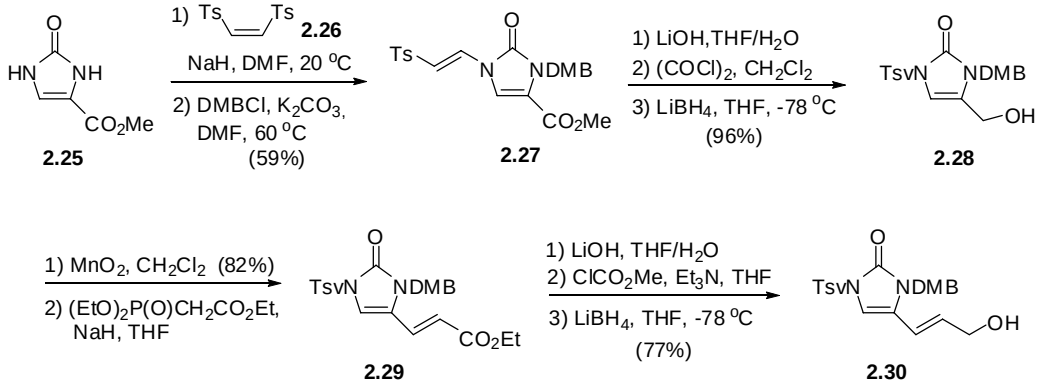
multiple roles including facilitating removal and altering reactivity.[45] Protecting groups that alter the electronic properties of substrates have also proven useful for a variety of reactions such as the Friedel-Crafts and Diels-Alder. The application of the electron withdrawing tosylvinyl (Tsv) group, which can be readily converted to the more electron rich tosylethyl (Tse) group, in our Diels-Alder/oxidation/ring contraction strategy towards the oroidin alkaloids is just another example of protecting groups being used for controlling regioselectivity and altering the substrate reactivity (*vide infra*).

C. Synthesis of Tsv-protected Diene

Synthesis of the Tsv-protected diene began with the known imidazolone methyl ester **2.25** (Scheme 11).[24] (Z)-1,2-di-*p*-toluenesulfonylethylene[46] (**2.26**) was used to install the Tsv group at the more accessible nitrogen (N1) on the imidazolone ring, via a presumed addition-elimination process. Protection of N2 with 3,4-dimethoxybenzyl chloride (DMBCl) gave the bis-protected imidazolone ester **2.27** in 59% overall yield for the two protection steps. Attempts to reduce the ester functionality in **2.27** directly to an alcohol using DIBAl-H, was successful but also led to concomitant reduction of the Tsv group to Tse. A more lengthy but efficient sequence involving hydrolysis to the acid, acid chloride formation, and reduction with lithium borohydride gave the desired alcohol **2.28** in 96% overall yield for the three steps. Oxidation to the corresponding aldehyde and Horner-Wadsworth-Emmons olefination gave ester **2.29** in 82% yield. Again, a three-step reduction sequence was required to prevent reduction of the Tsv group. Hydrolysis of the ester, followed by mixed anhydride formation, and treatment with

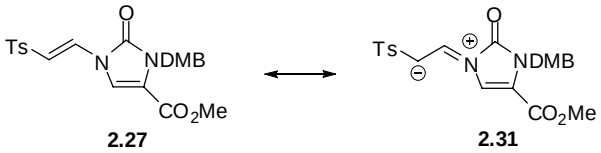
lithium borohydride provided dienyl alcohol **2.30** in 77% yield over the four steps and avoided reduction of the olefin in the Tsv group.

Scheme 11



During the efforts towards synthesis of diene **2.30**, it was found that the alkene functionality of the Tsv group could be reduced very easily with a stoichiometric amount of reducing agent, such as DIBAl-H, $NaBH_4$, or $BH_3 \cdot THF$. This is not surprising since that double bond is activated by the adjacent tosyl, a strong electron-withdrawing group (Scheme 12). The iminium species in the resonance structure **2.31** is even more reactive than an aldehyde. Therefore, in order to overcome the competing reduction of the Tsv alkene over the ester groups in **2.27** and **2.29**, the ester functionality had to be converted into more reactive species, i.e., an acid chloride or a mixed anhydride (Scheme 11).

Scheme 12



2.27 **2.31**

The synthesis of the Tsv-protected diene consists of 10 steps in total, which is lengthier than analogous dienes prepared previously.[24] The advantage of this route, however, is that no column chromatography purification is necessary throughout the ten-step sequence from imidazolone ester **2.25**, because of the easy purification at the acid stages by acid-base extraction.

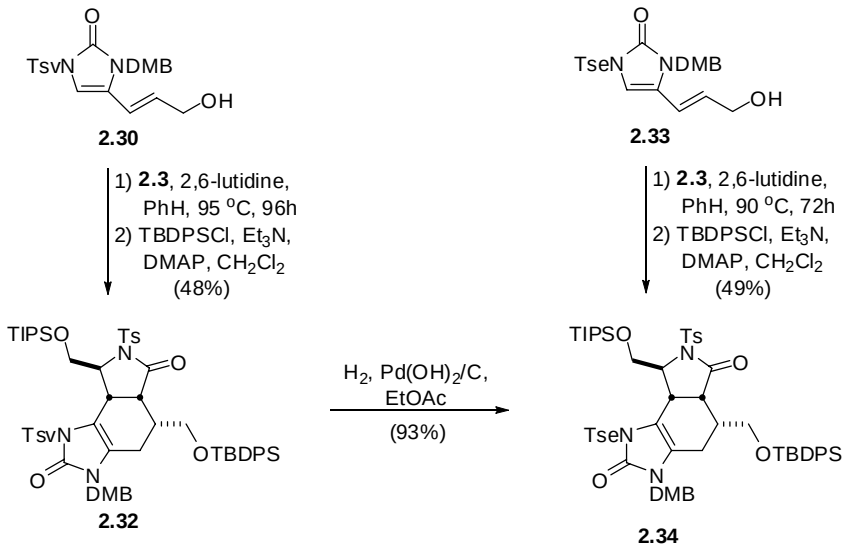
D. The Diels-Alder Reaction and Tsv Reduction

Heating diene **2.30** together with dienophile **2.3** in benzene at 95 °C for 96 h in the presence of 2,6-lutidine, pleasingly led to the formation of a single regioisomeric Diels-Alder adduct **2.32** in 48% overall yield following protection of the alcohol as the TBDPS ether (Scheme 13). Similar results were obtained using microwave irradiation at 175 °C for 45 min. In agreement with previous studies, the double bond in the initial adduct had migrated to regenerate the imidazolone ring under the reaction conditions. Interestingly, a further product was isolated which has been tentatively assigned as a Diels-Alder adduct from two units of the Tsv-diene, in which one of the Tsv groups has served as a dienophile. This side reaction accounts for the relatively low yield obtained from the Diels-Alder reaction of diene **2.30** and dienophile **2.3**. Most importantly, no

regioisomeric Diels-Alder adduct was observed from the reaction, proving the electron-withdrawing ability of Tsv group via vinylogous conjugation/induction effects.

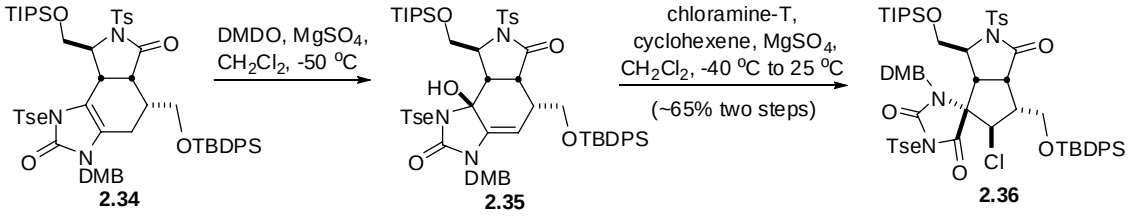
Reduction of the Tsv group was readily accomplished by hydrogenation to yield the Tse-protected Diels-Alder adduct **2.34** in excellent yield (Scheme 13). Corroboration of this structure was obtained by independent synthesis of the same compound from the Tse-protected diene **2.33**, which was prepared by a completely analogous process as that for diene **2.11** employing the mesylate of β-tosylethanol for N1 protection.[20] Diene **2.33** provided a 2.5:1 ratio of regioisomeric Diels-Alder adducts after the reaction, with the major product being the desired regioisomer. Subsequent alcohol protection afforded TBDPS-protected adduct **2.34**. NMR data comparison verified that the same Diels-Alder adduct had been obtained by the two routes.

Scheme 13



The use of the Tse-protected Diels-Alder adduct **2.34** in the oxidation and chlorination/1,2-shift resulted in the formation of the rearranged spirocycle **2.36** in an overall 65% yield over the two steps (Scheme 14), proving that the reduction of Tsv to Tse changed the electronics of the protecting group from electron-withdrawing to electron-donating, hence enabling the chlorination/1,2-shift cascade to occur.

Scheme 14



E. Conclusion

In summary, we have developed a strategy using an electronically adjustable protecting group to circumvent the need for a cumbersome protecting group switch. Importantly, this enabled a highly regioselective Diels-Alder process. While the efficiency of the Diels-Alder process using the Tsv-protected diene is not fully optimized, we anticipate that the concept of an electronically adjustable protecting group may find wider application in organic synthesis. The advanced spirocyclopentane **2.36** is a key intermediate in our synthetic efforts towards axinellamines and related oroidin-alkaloids.

CHAPTER III

STUDIES ON INSTALLATION OF THE α-CHLORO SUBSTITUENT FOR THE ORIGINALLY PROPOSED PALAU'AMINE STRUCTURE*

A. Introduction

Our interest in the oroidin alkaloids stemmed from the unique and complex structure presented by palau'amine in conjunction with its potent immunosuppressive activity. This falls into our group's interest in natural products displaying potent, cell-specific, physiological properties and the structurally distinct marine sponge isolates. Pateamine A, is an example of our continued interest in this field.[47] In the course of our studies toward the originally proposed palau'amine, a unified strategy towards both axinellamine and palau'amine was developed, proceeding through a Diels-Alder reaction and then diverging to axinellamine or palau'amine by means of either an inter- or intramolecular chlorination, respectively (Scheme 15).

This divergence addresses the difference in relative stereochemistry between the proposed structures of axinellamine (**1.19**) and palau'amine (**1.4**) at the chlorine bearing carbon C17 and also at C12. The *anti* relationship between C17 and C18 found in axinellamine could be accessed by intermolecular chlorination as a result of the topography of the tricyclic common intermediate **2.2**, obtained from a Diels-Alder process.[20,24] As previously shown, the oxidation/intermolecular chlorination/1,2-shift

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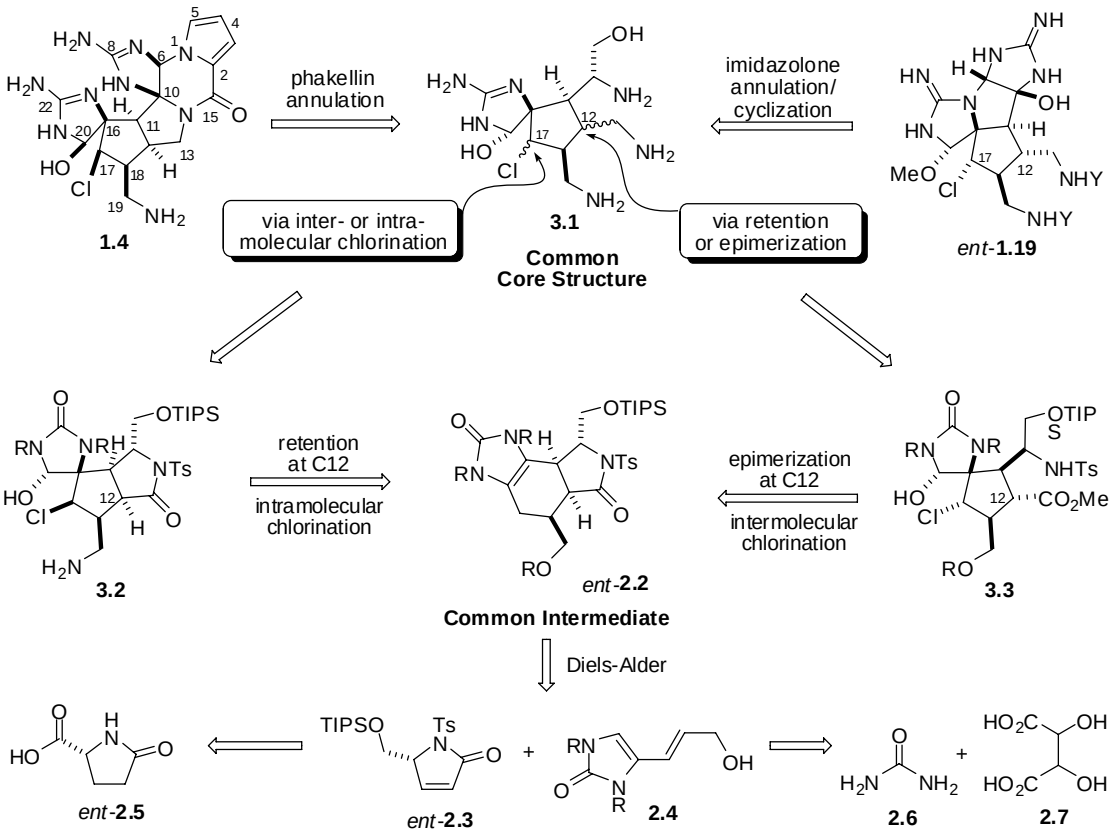
* Reproduced in part, with permission, from "Planned and Unplanned Halogenations in Route to Selected Oroidin Alkaloids" S. Wang, A. S. Dilley, K. G. Poullennec and D. Romo, *Tetrahedron* **2006**, *62*, 7155-7161; copyright 2006 by Elsevier Ltd.

sequence generated a chloro-cyclopentane structure possessing all the correct substituents and stereochemistry except for one stereocenter: C12 for axinellamine and C17 for palau'amine respectively (Chapter II, Scheme 14). A subsequent epimerization at C12 via enolization of a carbonyl functionality at C13 would be required to obtain the all *anti* configuration about the cyclopentane as found in axinellamine **1.19** (Scheme 15). Subsequent imidazolone annulation, guanidinylation, and an oxidative cyclization are proposed to form the final ring system and deliver axinellamine.

Scheme 15

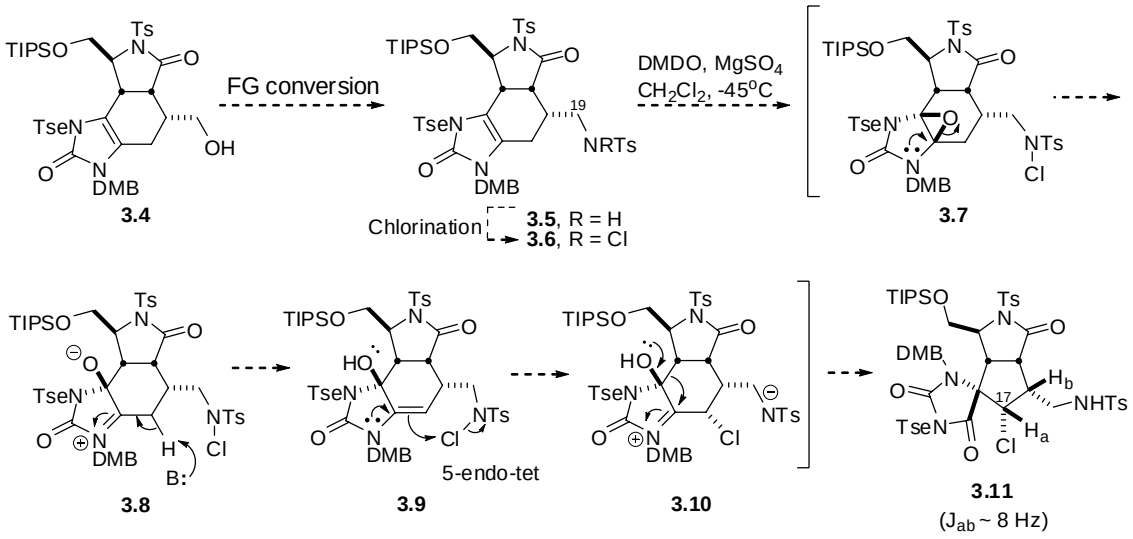


The chloro substituent of the cyclopentane **2.36** (Scheme 14), however, has the opposite stereochemistry for the originally proposed palau'amine (**1.4**). To address this problem, an intramolecular chlorination would be reasonable to set the required stereochemistry at C17 after DMDO oxidation of the Diels-Alder adduct **2.2**. The cycloaddition has already set the required *syn* stereochemistry at C11 and C12, thus epimerization at C12 is not required. Guanidinylation and annulation of the phakellin substructure onto core structure **3.2** would deliver palau'amine (Scheme 15).

B. Intramolecular Chlorination Studies

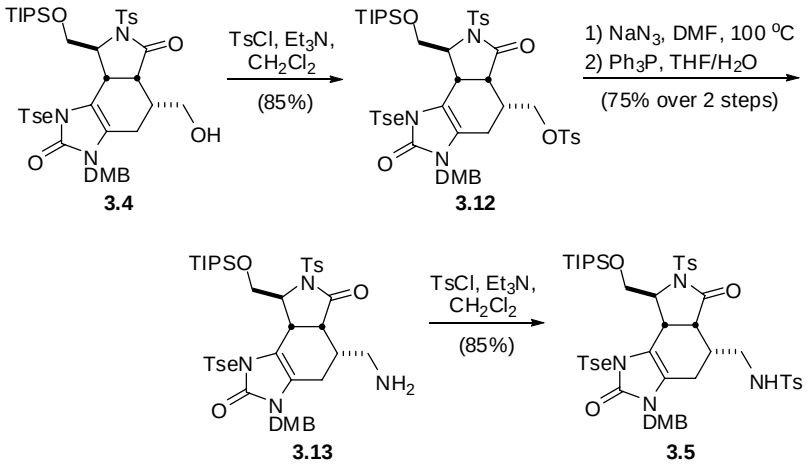
Installation of a sulfonamide at the C19 position would be necessary for an intramolecular chlorination process. After functional group conversions, a chlorinated *p*-toluenesulfonamide **3.6** might be accessible from the Diels-Alder adduct **3.4** (Scheme 16). DMDO oxidation would trigger a cascade reaction including epoxidation, epoxide ring opening, deprotonation, intramolecular chlorination and 1,2-shift, delivering the desired stereochemistry. We envisioned this pendant electrophilic chlorine source, i.e. the chloro-*p*-toluenesulfonamide, would deliver the chlorine in an intramolecular fashion to the concave face of tricycle **3.9** to yield cyclopentane **3.11** following ring contraction. This strategy is reminiscent of an intramolecular, directed chlorination reported by Breslow.[48] While the proposed 5-endo-tet transition state would be an exception to Baldwin's rule,[49] there are numerous exceptions including attack at heteroatoms.[50] The desired α-chloro spirocycle **3.11** should have a coupling constant of 8 Hz between H_a and H_b as shown in Scheme 16.[39]

Scheme 16



Synthesis of the substrate (**3.5**) for the intramolecular chlorination studies began with Diels-Alder adduct **3.4**. Tosylation of the primary alcohol, followed by displacement of the tosylate by an azide and reduction of the azide afforded a primary amine **3.13** (Scheme 17). The amine was then converted to a *p*-toluenesulfonamide **3.5**. Direct azide formation from alcohol **3.4** via Mitsunobu conditions was unsuccessful. Attempts to displace the tosylate functional group in **3.12** directly with tosylamine to form sulfonamide **3.5** also failed.

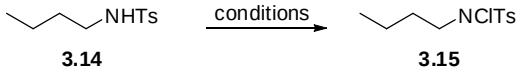
Scheme 17



Although there are literature precedents about *N*-chlorination of *p*-toluenesulfonamide and other amides,[51] it was still desirable to carry out a model study on this reaction, and a simple *n*-butyl-*p*-toluenesulfonamide **3.14** was selected as the model system (Table 2). *N*-Chlorosuccinimide (NCS) was not able to chlorinate **3.14**, even after deprotonation of the amide. Apparently the tosyl group is more electron-withdrawing than the double carbonyls in NCS, making the nitrogen anion in the deprotonated **3.14** less nucleophilic than the succinimide nitrogen anion. Chloramine-T did not work either. The reagents that were able to convert **3.14** to **3.15** were *t*-butylhypochlorite, trichloroisocyanuric acid (TCIA) and 2,3,4,5,6,6-hexachloro-2,4-cyclohexadiene-1-one (HCCO) (Table 2). The chlorinated sulfonamide **3.15** can be reduced easily by dimethylsulfide and is not stable to silica gel chromatography. Both *t*BuOCl and TCIA were able to chlorinate **3.14** without deprotonation of the sulfonamide. In the real system **3.5**, however, deprotonation would be necessary to generate a more nucleophilic

nitrogen anion, which we expected to be more reactive towards chlorine cation source than the electron-rich double bond in the imidazolone ring moiety.

Table 2. Model studies on *N*-chlorination



3.14 **3.15**

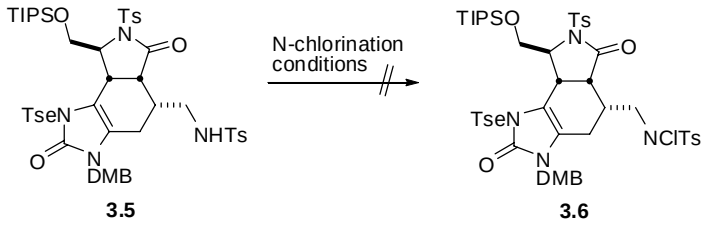
entry	conditions	results [a]
1	NaH, THF; NCS	S.M.
2	*n*BuLi, THF, -78 °C; NCS	S.M.
3	*n*BuLi, THF, -78 °C; chloramine-T	S.M.
4	*n*BuLi, THF, -78 °C; *t*BuOCl	95%
5	*t*BuOCl, CH_2Cl_2, -78 °C	91%
6	*n*BuLi, THF, -78 °C; TCIA	100%
7	*n*BuLi, THF, -78 °C; HCCO	75%

a: percent conversion by NMR analysis

With these results in hands, chlorination of sulfonamide **3.5** was studied, but disappointingly, none of those conditions gave the desired product **3.6** (Scheme 18). When the reactions were carried out at -78 °C, no chlorination was observed (starting material was recovered). At higher temperatures (-50 °C, 20 °C), side products that presumably resulted from the reactions of the chlorinating agents with the electron-rich double bond in imidazolone ring were formed predominantly. In fact, sulfonamide **3.5** is not even compatible with *N*-chlorosulfonamide functionality. When sulfonamide **3.5** was treated with *N*-chlorosulfonamide **3.15**, an unidentified complex mixture of products was formed, suggesting that the substrate reacts with the chlorinating reagent to form undesired products, or that even though the desired product **3.6** could be formed under

the chlorination condition, it is not stable and can undergo degradation easily via intermolecular reactions with itself.

Scheme 18

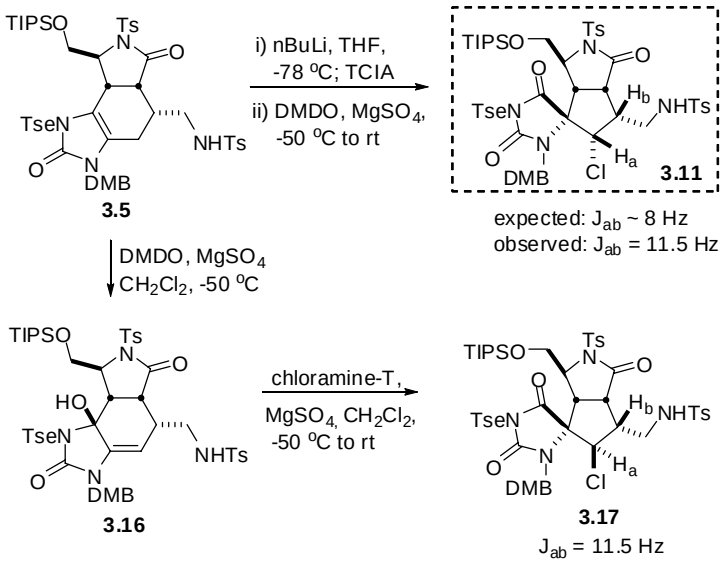


3.5 **3.6**

With the consideration that *N*-chlorosulfonamide **3.6** might be generated *in situ* but could not be isolated due to its instability, a one-pot *N*-chlorination/oxidation/1,2-shift reaction was tried with sulfonamide **3.5** (Scheme 19). A rearranged compound with the same molecular mass as desired compound **3.11** was isolated. If the chlorine stereochemistry was correct, a coupling constant of 8 Hz between Ha and Hb should have been observed.[39] However the observed coupling constant J_{ab} was 11.5 Hz, indicating the chlorine was on the β-face, as in **3.11**'s diastereoisomer **3.17**. Through known intermolecular chlorination procedures, **3.17** was synthesized independently via allylic alcohol **3.16**, and was identical, based on spectra data comparision, with the product isolated from the aforementioned one-pot reaction. This result indicated that the desired intramolecular chlorination/1,2-shift did not occur and the product isolated from that reaction was actually β-chlorocyclopentane **3.17**. The formation of **3.17** was probably a result of more facile intermolecular chlorination/1,2-shift reaction between allylic alcohol **3.16** generated *in situ* with chlorinating agent trichloroisocyanuric acid

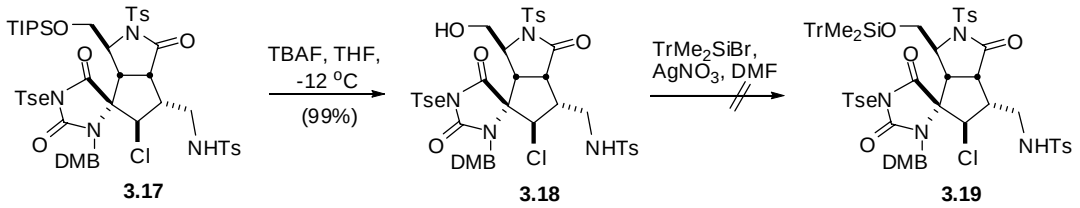
(TCIA). The same one-pot reaction was tried again in highly diluted solution (0.6 mM in THF), but resulted in mainly recovered starting material with trace amount of β-chlorinated product **3.17**.

Scheme 19



β-Chlorocyclopentane **3.17** is a foam, and cannot form crystals. In an attempt to obtain a crystal structure of the β-chlorinated cyclopentane core structure, **3.17** was desilylated with TBAF (Scheme 20) and the resulting alcohol was treated with trityldimethylbromosilane to form a trityldimethylsilyl protected compound, which is known to form crystals readily.[52] Unfortunately, the desired product was not observed under such reaction conditions.

Scheme 20



Molecular modeling studies showed the main reason behind these unsuccessful attempts on intramolecular chlorination. In an energy minimized 3D model of the chlorination intermediate **3.9** (protecting groups are removed for clarity), one can clearly see that the central six-membered ring is in a boat conformation, and the chlorine atom on the sulfonamide nitrogen is far away from the projected reaction site, i.e., the enamine terminal carbon (Figure 10). It would be energy demanding for the chloro-sulfonamide group to go under the concave face of the tricyclic structure.

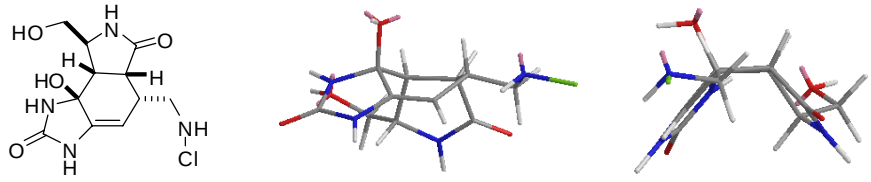


Figure 10. Molecular modeling of the chlorination intermediate

C. Effects of the Tosyl Protecting Group

In the molecular model of allylic alcohol intermediate **3.20** prior to chlorination, the tosyl protecting group on the lactam nitrogen resides beneath the concave face of the

tricyclic system, blocking chlorinating reagents from reaching the sp^2 enamine carbon reaction center (Figure 11). On the other hand, the convex face of the molecule is open to chlorinating reagents without any steric hindrance. If the tosyl group was removed (**3.21**), the concave face of the allylic alcohol would be more open to chlorinating reagents, hence making chlorination on both the convex face and the concave face possible, generating mixture of β-chloro and α-chloro cyclopentane products. Once this hypothesis was validated, the allylic alcohol in **3.21** could be protected by TMS, to generate steric hindrance on the convex face, therefore making chlorination happen on the concave face to form α-chloro cyclopentane product.

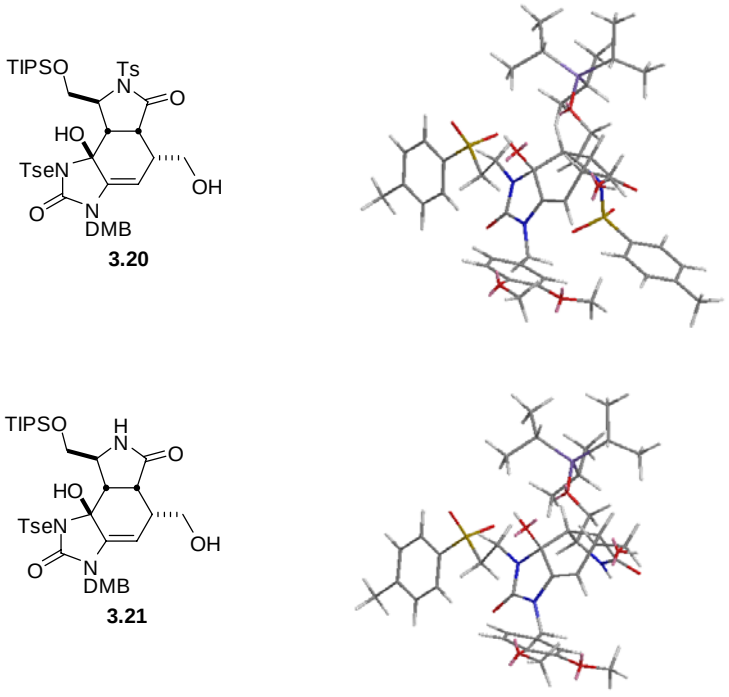
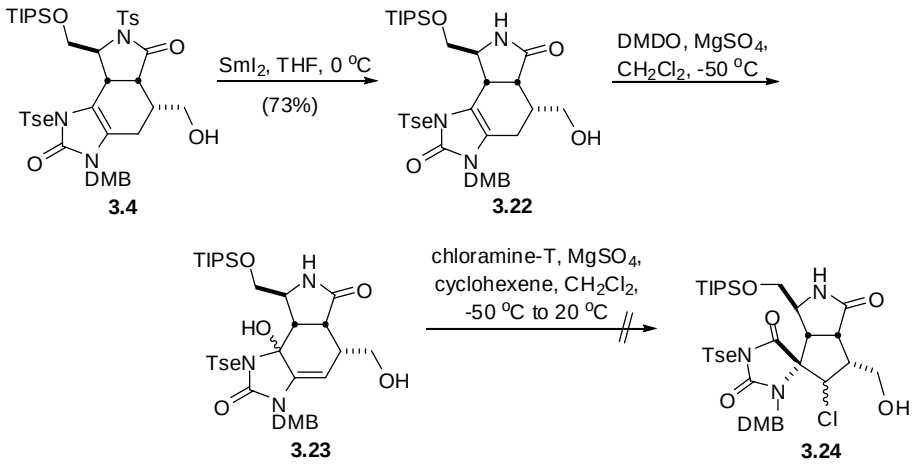


Figure 11. Molecular models of allylic alcohols prior to chlorination

After detosylation of the Diels-Alder adduct **3.4**,[53] lactam **3.22** was oxidized to give allylic alcohol **3.23**, resulting in a mixture of two diastereomers, as expected (Scheme 21). The crude product from the oxidation was subjected to the chlorination/ ring contraction conditions, but did not yield the desired diastereomeric mixture of chlorinated products **3.24**.

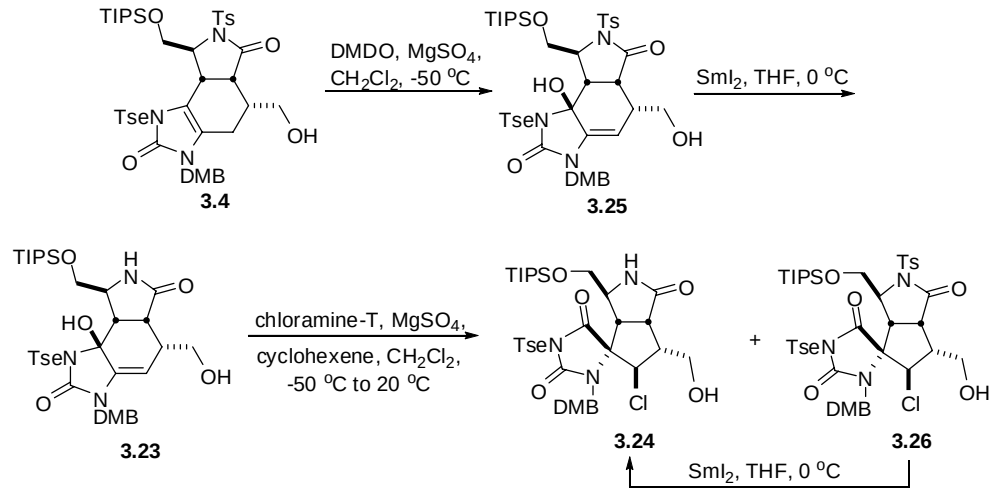
Scheme 21



To circumvent the problem of generating diastereomers of the allylic alcohol **3.23**, Diels-Alder adduct **3.4** was first oxidized to form allylic alcohol **3.25** as a single diastereomer (Scheme 22), which was then detosylated to give allylic alcohol **3.23**. Subsequent chlorination, disappointingly, gave only the β-chloro product **3.24**. Some β-chlorocyclopentane **3.25** was also isolated from the chlorination reaction, due to some unreacted allylic alcohol **3.25** in the detosylation step. The identity of compound **3.24** was further confirmed by spectral data comparison with the detosylation product of β-

chlorocyclopentane **3.26**. No α-chlorination was observed on substrate **3.23**, suggesting that the chlorinating reagent still approaches the allylic alcohol intermediate from the convex face, even without a tosyl group blocking the concave face.

Scheme 22

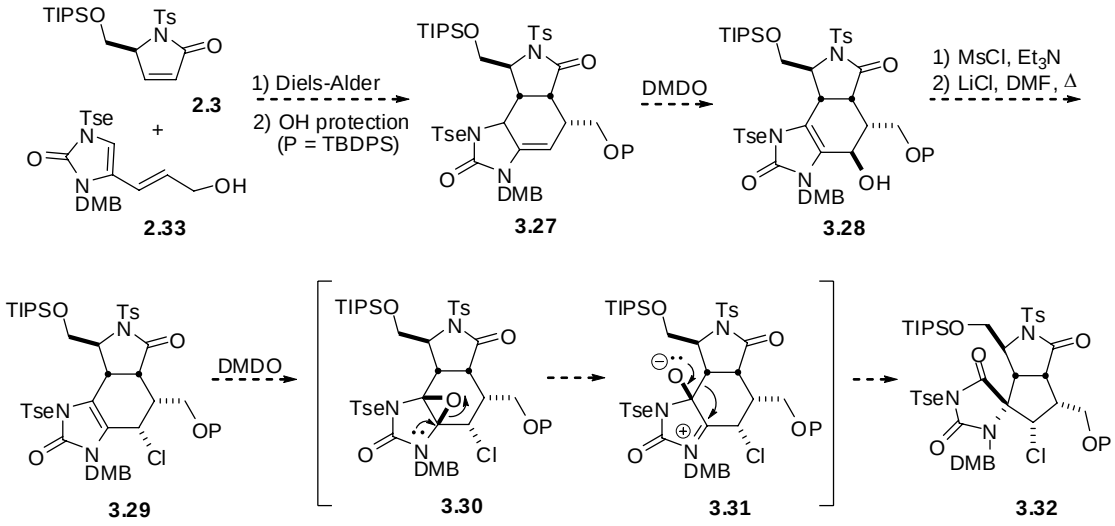


D. Studies on the Initial Diels-Alder Adduct

While experiencing difficulties on directed intramolecular chlorination, various other methods to install the α-chlorine were investigated. One alternative way to obtain the α-chloro spirocyclic structure was proposed as shown in Scheme 23. The Diels-Alder reaction of dienophile **2.3** and Tse-diene **2.33** could be optimized in such a way that the initial Diels-Alder adduct **3.27** was formed as the major product. According to Lovely's observations in a similar system,[25d] silyl protected adduct **3.27** can be oxidized to allylic alcohol **3.28**. Mesylation of the alcohol will make the hydroxyl group a good leaving group, after which α-chlorine can be installed via S_N2 displacement of the

mesylate intermediate. The subsequent second DMDO oxidation will give intermediate **3.30**, which may rearrange to give desired α-chloro cyclopentane structure (**3.32**) for palau'amine.

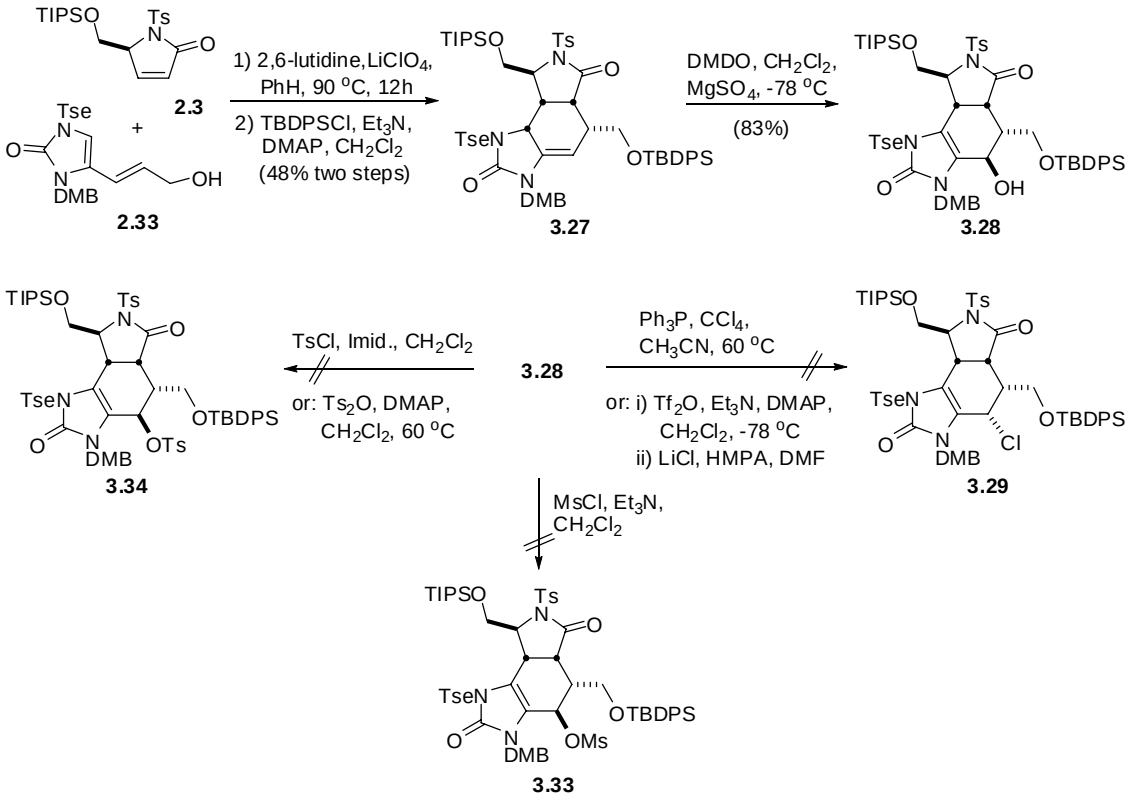
Scheme 23



Under careful control of the reaction time, the Diels-Alder reaction did give the proposed initial Diels-Alder adduct along with its inseparable regioisomer. Following immediate protection of the primary alcohol by TBDPSCl, adduct **3.27** could be isolated from its regioisomer and was obtained in 48% yield over the two steps (Scheme 24). Treatment with one equivalent of DMDO successfully generated allylic alcohol **3.28**, but unfortunately, the following transformation to form the proposed chloro-cyclohexene intermediate **3.29** failed under various conditions. Attempts on converting the allylic alcohol **3.28** to its corresponding mesylate **3.33** or tosylate **3.34** were not successful either. A complex mixture of products was often observed during these reactions,

presumably due to the reactivity of the allylic alcohol functionality, which might undergo elimination easily and further degrade to aromatic compounds.

Scheme 24

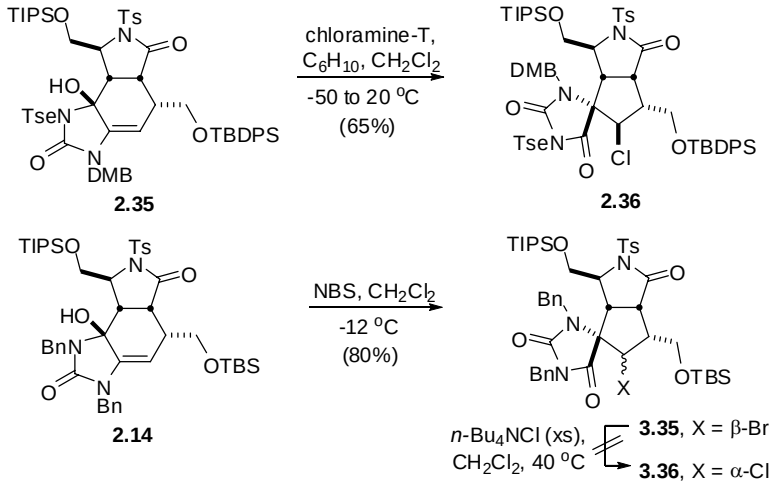


E. Studies on S_N2 Displacement of β-Iodides

As previously shown, subjecting allylic alcohol **2.35** to chloramine-T causes an intermolecular, stereoselective chlorination and a concomitant suprafacial 1,2-shift/ring contraction to yield functionalized chlorocyclopentane **2.36** (Chapter II, Scheme 14). This cyclopentane contains five stereocenters, identical to the proposed structure of axinellamine with the exception of C12. The high stereoselectivity of the chlorination is

due to the distinctly cup-shaped topology of allylic alcohol **2.35**. In order to install the stereochemistry at the chlorine center C17 as proposed for palau'amine (Scheme 15), which is opposite to that of axinellamine, a reverse Finkelstein strategy involving S_N2 displacement of an appropriate leaving group such as bromide or iodide, was considered. Bromination of allylic alcohol **2.14** with *N*-bromosuccinimide also initiated the ring contraction process and delivered β-bromocyclopentane **3.35** (Scheme 25). However, attempts to displace the bromide with excess chloride anion under a variety of conditions led to no reaction. [39]

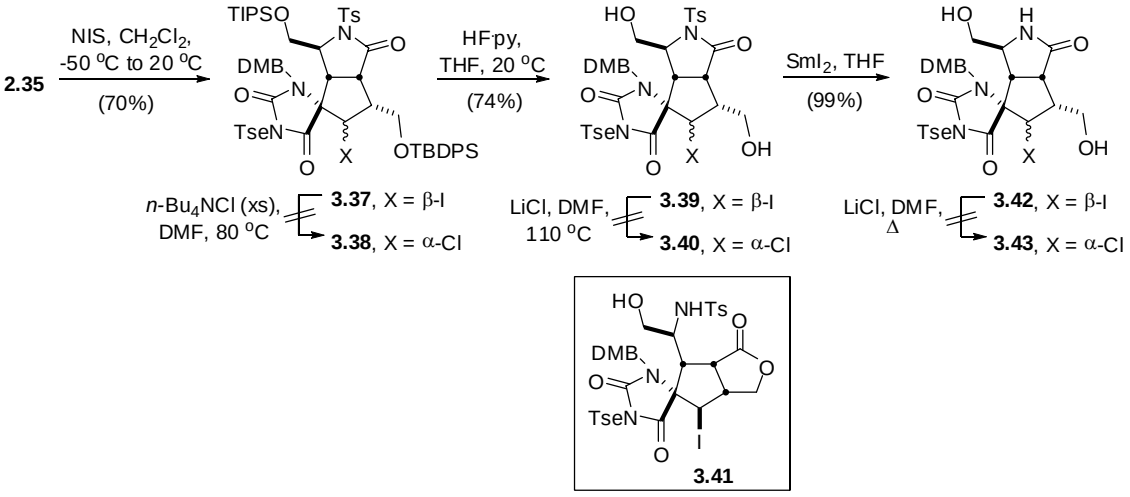
Scheme 25



Allylic alcohol **2.35** could also be iodinated and following ring contraction provided β-iodocyclopentane **3.37** (Scheme 26). Iodide **3.37** was prepared with the expectation that this compound may undergo a more facile reverse Finkelstein process under forcing conditions; however no displacement was observed under several

conditions to provide the desired α-chloro compound **3.38**. Silyl deprotection was attempted to remove any steric hindrance, however this did not facilitate the projected displacement. α-Chloro cyclopentane **3.40** was not observed under forcing conditions; instead, the only observed product in this case was lactam opening by the pendant alcohol to deliver lactone **3.41**. To prevent lactam cleavage, the *N*-tosyl group was removed to give free lactam **3.42**,[53] but unfortunately further attempts to chlorinate were also unsuccessful. The stability of these spirocyclic systems toward S_N2 displacement by chloride anion is likely due to steric issues since the nucleophile must enter the concave face with an adjacent spiro quaternary center for an S_N2-type process.

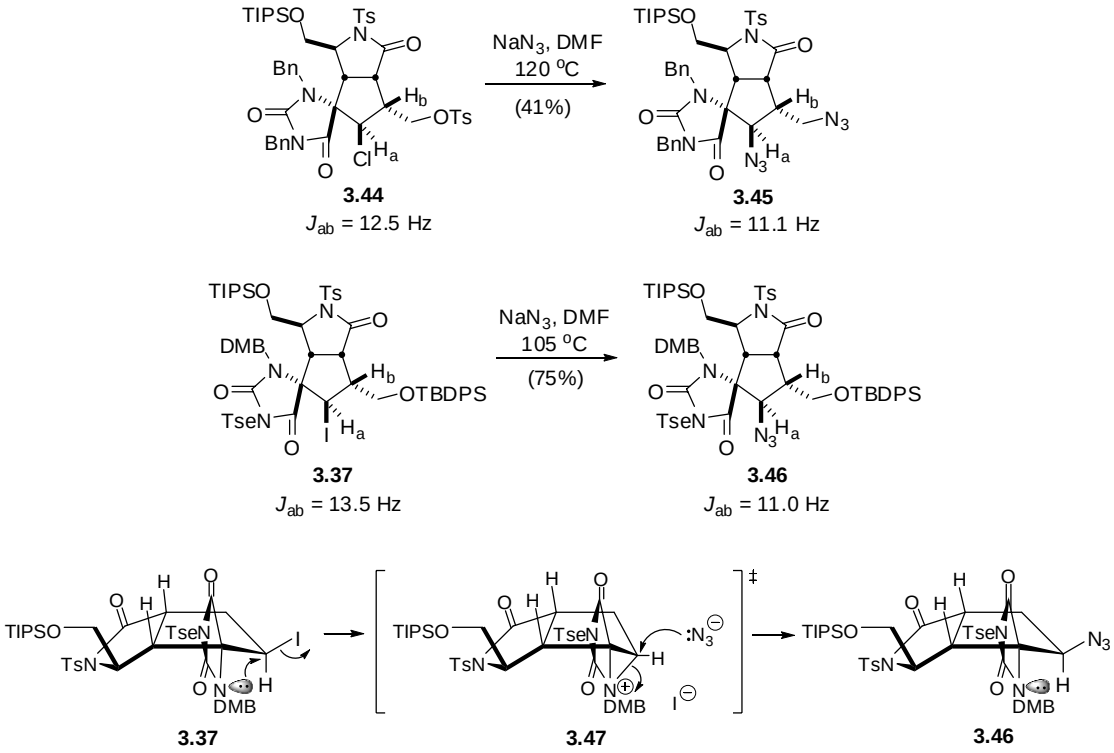
Scheme 26



Chloride displacement was ultimately achieved unexpectedly during conversion of the pendant tosylate of spirocycle **3.44** to an azide during studies toward axinellamine.[39] The chlorine atom was also displaced concomitantly but surprisingly

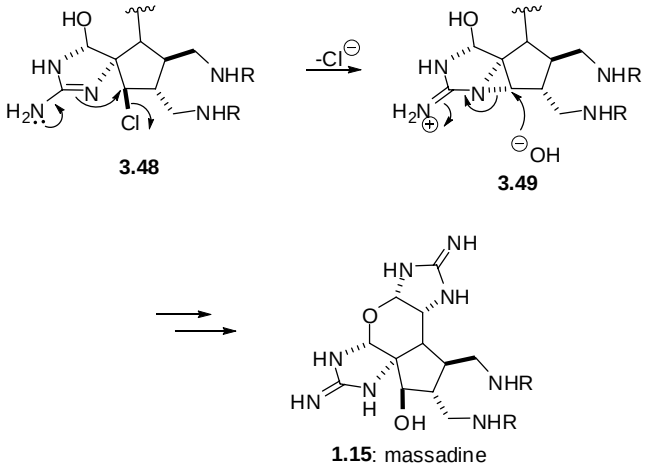
with retention of configuration, as determined by coupling constant analysis, to yield bisazide **3.45** (Scheme 27). As expected, displacement of iodide in spirocycle **3.37** was more facile and led to higher yields of the corresponding azide **3.46.** Retention of configuration may be rationalized by invoking neighboring group participation proceeding through an aziridinium intermediate **3.47** (Scheme 27). Under heating condition, intramolecular substitution by the proximal, benzylated nitrogen atom, which appears well situated to displace the iodide of spirohydantoin **3.37**, leads to net retention of configuration upon ring opening of the aziridinium by azide nucleophile.

Scheme 27



Considering the relative facility of this process with spirohydantoins **3.44** and **3.37**, it is reasonable to speculate that this type of transformation may be a more facile process with the electron rich cyclic guanidine found in these natural products (e.g. **3.48**), especially under the catalysis of enzymes. Thus, a possible biosynthetic pathway leading to massadine[31] may involve a related retentive displacement of a chloride from the chloro-derivative of massadine **3.48**, followed by ring opening of the aziridine by water and ultimately leading to massadine **1.15** (Scheme 28). A related process was recently proposed for the natural product fasicularin.[54] Same type of pathway could be drawn for the biogenesis of dimeric massadine derivatives: stylissadine A and B (**1.39**, **1.40**), in which a second molecule of massadine acts as a nucleophile to open the aziridine ring system in intermediate **3.49** to form stylissadines. Recent isolation and chemical derivatization studies of massadine chloride (**1.41**) also provided evidence for this proposal.[32]

Scheme 28



F. Conclusion

In efforts to achieve the correct stereochemistry at C17 for the originally proposed palau'amine structure, an intramolecular, directed chlorination was studied, based on previously achieved chlorination/ring contraction sequence leading to the highly functionalized chlorocyclopentane core structure of axinellamine and related oroidin alkaloids. However, this projected intramolecular chlorination did not give the desired α-chloro product. Instead, exclusive intermolecular chlorination was observed. Attempts to obtain a α-chloro spirocycle through initial Diels-Alder adduct did not meet with success either. In an alternative way to install the α-chloro substituent on C17, the previously developed intermolecular chlorination process was extended to provide β-brominated and β-iodinated cyclopentanes. Subsequent attempts on S_N2 displacement of these halogens by excess chloride anion were unsuccessful. An unexpected displacement of chloride/iodide by azide anion proceeding with retention of configuration prompted us to propose a related process in the biogenesis of massadine and stylissadines. These results proved that installing the α-chloro substituent on C17 of the originally proposed palau'amine structure is a highly challenging task. Even though the recent structural revision of palau'amine pointed out that the stereochemistry of C17 was misassigned (Chapter I, section E), making the efforts described here futile, many intriguing aspects of oroidin-alkaloid chemistry were explored, and findings from these studies provided useful information for further synthetic efforts towards palau'amine and axinellamine.

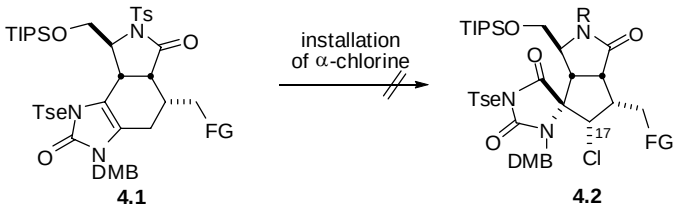
CHAPTER IV

SYNTHESIS OF AN ADVANCED PENTACYCLIC INTERMEDIATE TOWARD EPI-PALAU'AMINE

A. Introduction

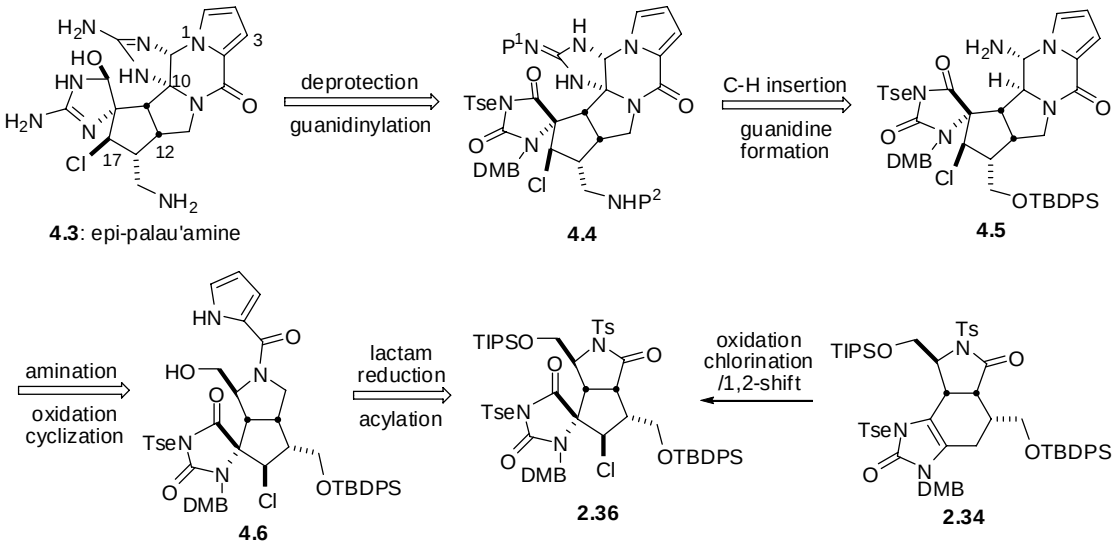
Due to its structurally complex nature, palau'amine has thus far eluded total synthesis, despite much attention from synthetic chemists. Few reports have been published regarding the synthesis of palau'amine,[12] although there are at least ten research groups working on this subject. The synthetic challenges of palau'amine continue to drive us on the adventure of making palau'amine.[20,24] After extensive studies on the installation of the α-chlorine substituent onto the central cyclopentane moiety without success (Scheme 29), we decided to pursue the synthesis of presumed epi-palau'amine with a β-chlorine on C17 (**4.3**, Scheme 30). The completed synthesis of epi-palau'amine would serve the purpose of verifying palau'amine's structural assignment and also provide a synthetic platform for the derivatization of palau'amine for structure-activity relationship investigations.

Scheme 29



The planned synthesis of epi-palau'amine started with chlorocyclopentane **2.36** (Scheme 30). Now that we had all the three ring systems of the lower hemisphere of palau'amine, the remaining tasks were phakellin annulation, guanidinylation and late stage functional group manipulation (Chapter II, Scheme 6). Phakellin annulation strategy involves a few key transformations such as pyrrole acylation, reduction of the lactam, oxidation/cyclization, installation of guanidine and C-H insertion (*vide infra*).

Scheme 30



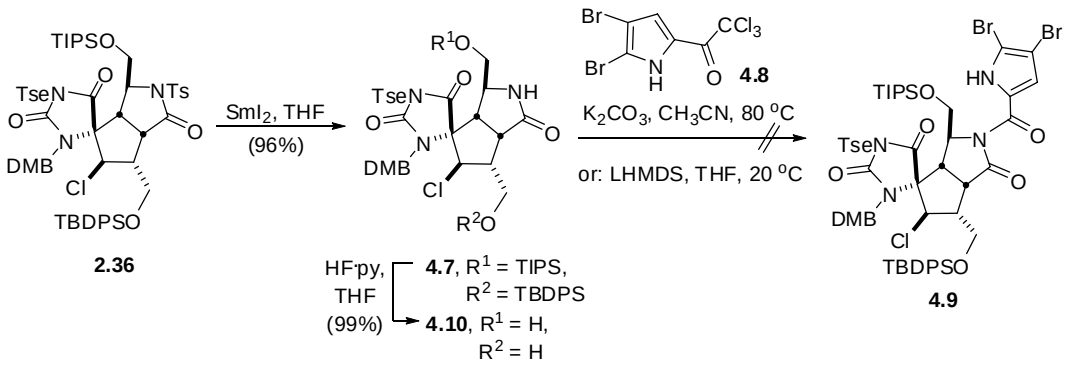
B. Pyrrole-acylation Studies

1. Pyrrole-acylation Attempts before Lactam Reduction

The spirocyclic β-chlorine-containing intermediate **2.36** could be obtained in around 65% yield over two steps from TBDPS-protected Diels-Alder adduct **2.34** via oxidation/chlorination/1,2-shift cascade (Chapter II, Scheme 14). Removal of the tosyl

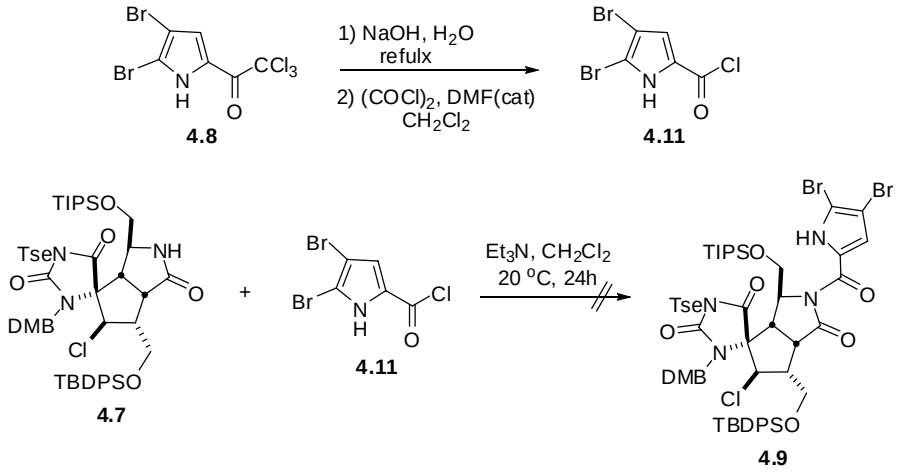
group from the lactam ring in compound **2.36** was accomplished by using SmI_2 in THF. 4,5-Dibromo-2-trichloroacetylpyrrole **4.8** was prepared from the readily available 2-trichloroacetylpyrrole via bromination.[55] Acylation attempts of chlorocyclopentane **4.7** with trichloroacylpyrrole **4.8** were unsuccessful under the two typical conditions shown in Scheme 31, probably due to the insufficient reactivity of both the nucleophile and the electrophile. (In an attempt to get a crystal structure of a chlorocyclopentane, **4.7** was deprotected with HF to give diol **4.10**. However, diol **4.10** did not form crystals.)

Scheme 31



To improve the reactivity of the electrophile, trichloroacylpyrrole **4.8** was hydrolyzed into an acid and subsequently converted to an acid chloride **4.11** (Scheme 32).[56] However, the attempt to couple the acid chloride with the lactam **4.7** failed again to yield the desired pyrrole-acylated product **4.9**, as shown by NMR data.

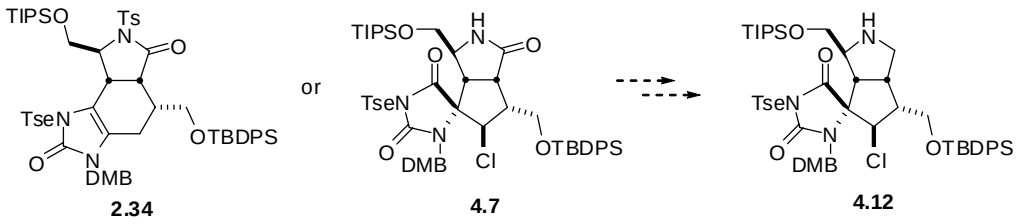
Scheme 32



2. Pyrrole-acylation after Lactam Reduction

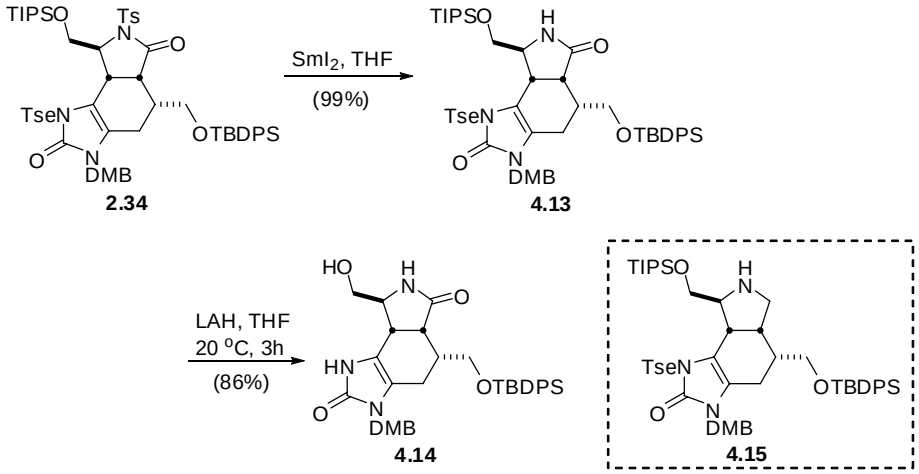
Unsuccessful attempts to acylate the lactam nitrogen in lactam **4.7** warranted the reduction of the lactam to a pyrrolidine, since the pyrrolidine nitrogen would be more nucleophilic and easier to be acylated. Reduction of the lactam could be carried out either before the oxidation/chlorination on the protected Diels-Alder adduct **2.34** or after the formation of chlorocyclopentane **4.7** (Scheme 33). The first route was studied initially.

Scheme 33



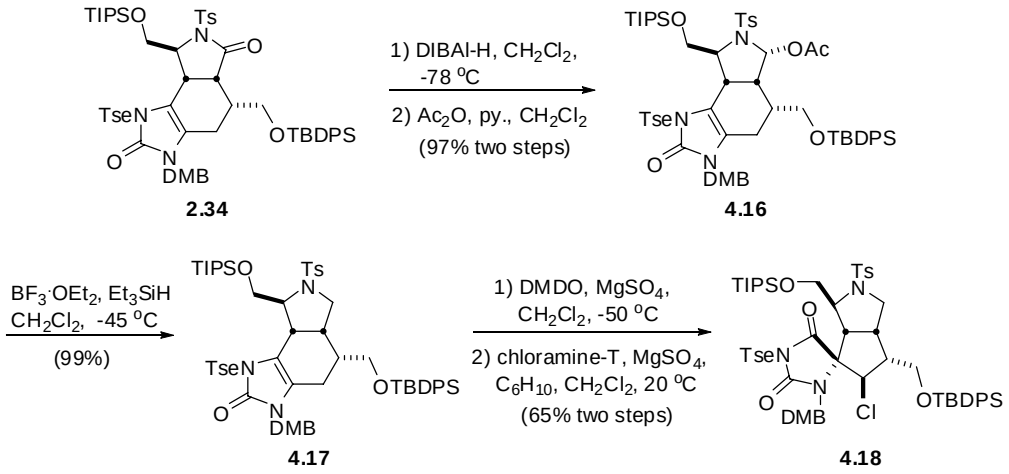
Silyl protected Diels-Alder adduct **2.34** was detosylated with SmI_2 to give lactam **4.13** quantitatively. However, the lactam reduction using known conditions[57] did not give the desired pyrrolidine product **4.15** (Scheme 34). The isolated product was characterized as alcohol **4.14**, where both the TIPS and Tse protecting groups were removed, probably during the workup process.

Scheme 34



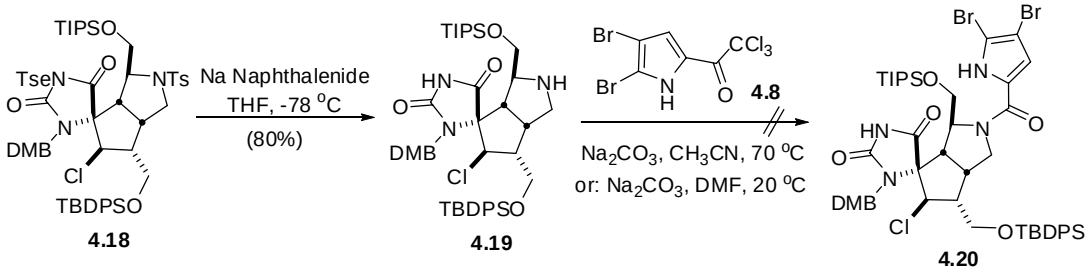
Redutction of the lactam was finally achieved via a three-step sequence. DIBAl-H reduction of lactam **2.34** to the corresponding aminal, acetylation and subsequent BF_3 mediated reduction afforded the tosyl-protected pyrrolidine **4.17** in high yield over three steps (Scheme 35).[58] The oxidation/chlorination/1,2-shift sequence also worked on the deoxygenated compound **4.17** (Scheme 6), yielding the desired chlorocyclopentane ring system **4.18**. This observation was contrary to the result obtained from an earlier study in the group.[39]

Scheme 35



Detosylation of chlorocyclopentane **4.18** using sodium naphthalenide at low temperature gave product **4.19**,[59] with Tse also being removed concomitantly. Acylation in CH_3CN under heating conditions gave degraded material. A second attempt to acylate pyrrolidine **4.19** in DMF did not give the desired product either, based on NMR and MS analysis (Scheme 36).

Scheme 36



A 3D model of compound **4.19** (Figure 12) shows that the TIPS protecting group is blocking the β-face of the pyrrolidine, while the α-face is congested. So it would be necessary to remove the TIPS group selectively before the acylation of the pyrrolidine. This seemingly trivial step[60] actually failed under various conditions, yielding either a mixture of products as a result of nonselective desilylation or completely desilylated product (Scheme 37). Attempts to selectively remove the TIPS group from analogous compound **4.18** before detosylation were also unsuccessful.

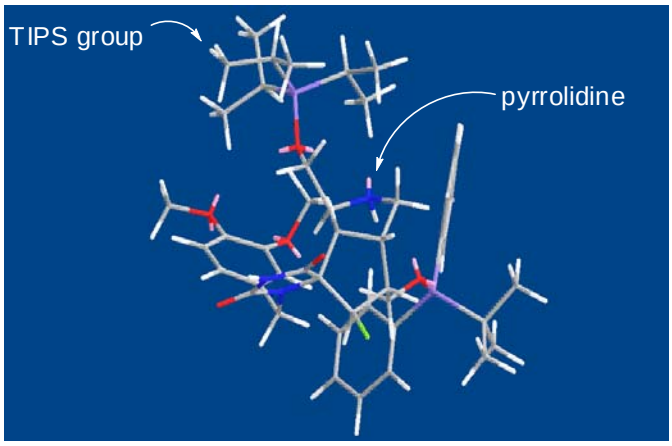
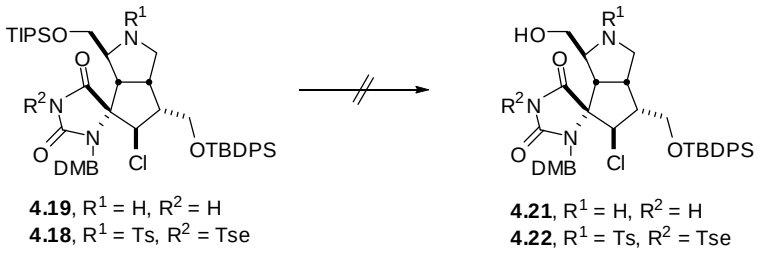


Figure 12. Molecular modeling of pyrrolidine **4.19**

Scheme 37

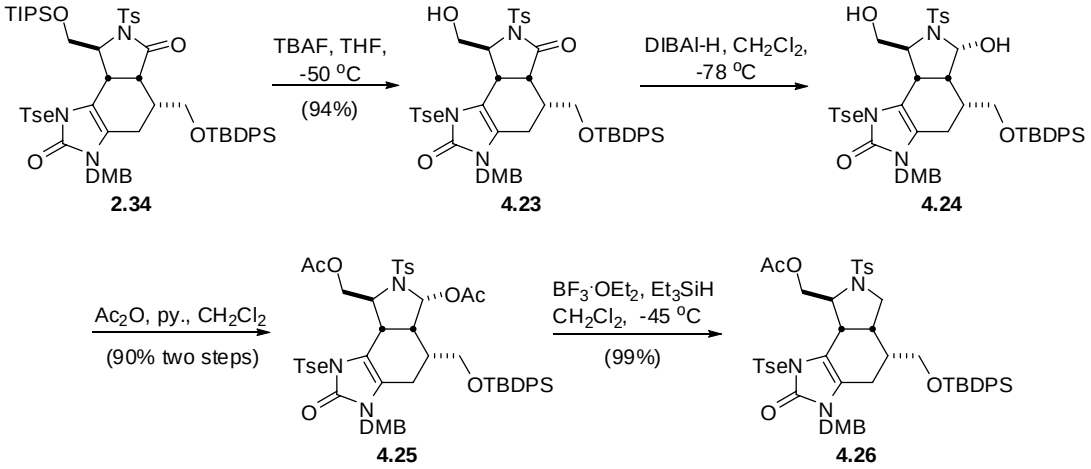


4.19, R^1 = H, R^2 = H
4.18, R^1 = Ts, R^2 = Tse

4.21, R^1 = H, R^2 = H
4.22, R^1 = Ts, R^2 = Tse

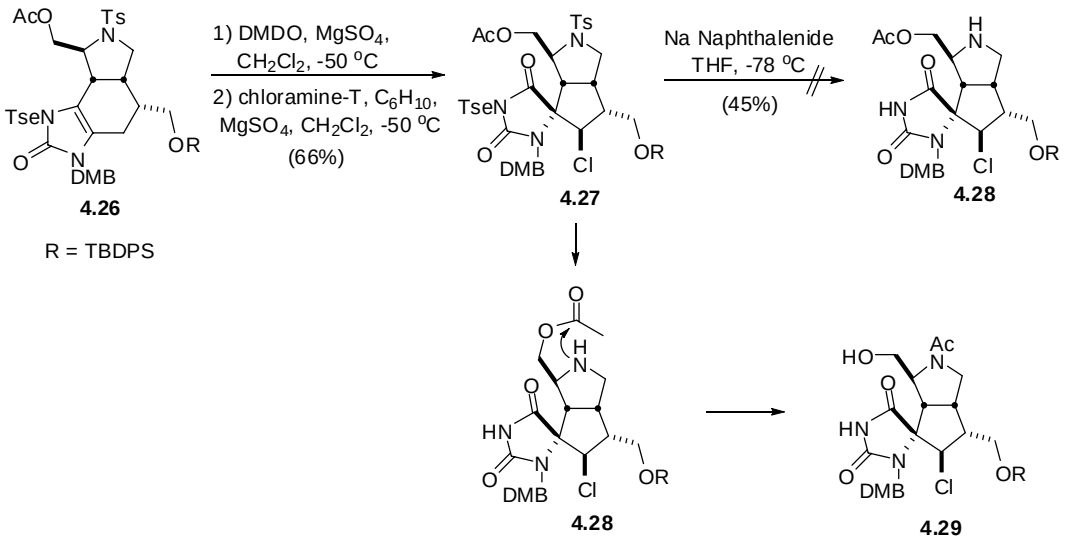
While selective desilylation could not be achieved on substrate **4.18**, the TIPS group in Diels-Alder adduct **2.34** could be easily cleaved without affecting the TBDPS group (Scheme 38). The resulting compound **4.23** was converted to the protected pyrrolidine **4.26** successfully via the three-step process used to prepare pyrrolidine **4.17**.

Scheme 38



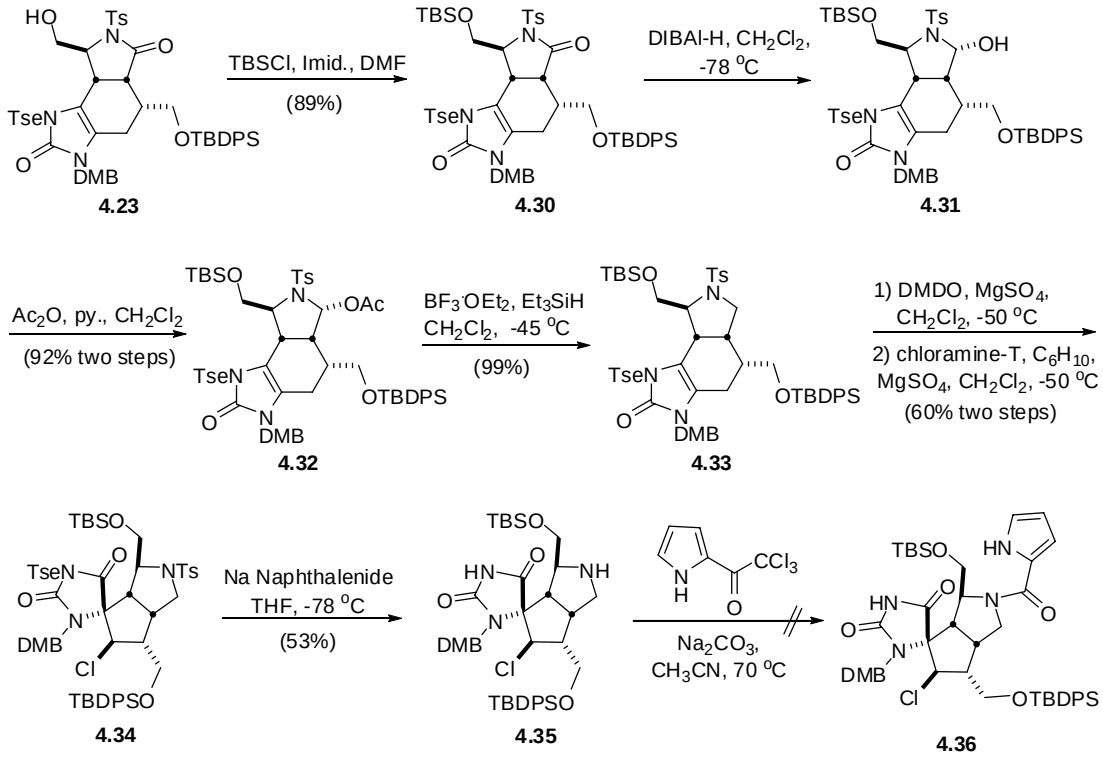
The following oxidation/chlorination/rearrangement sequence gave chlorinated compound **4.27** with some inseparable aromatic by-product (Scheme 39). Subsequent sodium naphthalenide condition gave the detosylated product in less than 45% yield. However, further studies revealed that the product was not the desired acetate pyrrolidine **4.28**, but actually an acetamide (**4.29**), which was formed *in situ* directly after the removal of the tosyl group via intramolecular acetyl transfer. The acetyl group in acetamide **4.29** could not be removed under various conditions. To prevent the acetyl transfer onto pyrrolidine nitrogen, protection of the primary alcohol after TIPS removal was necessary.

Scheme 39



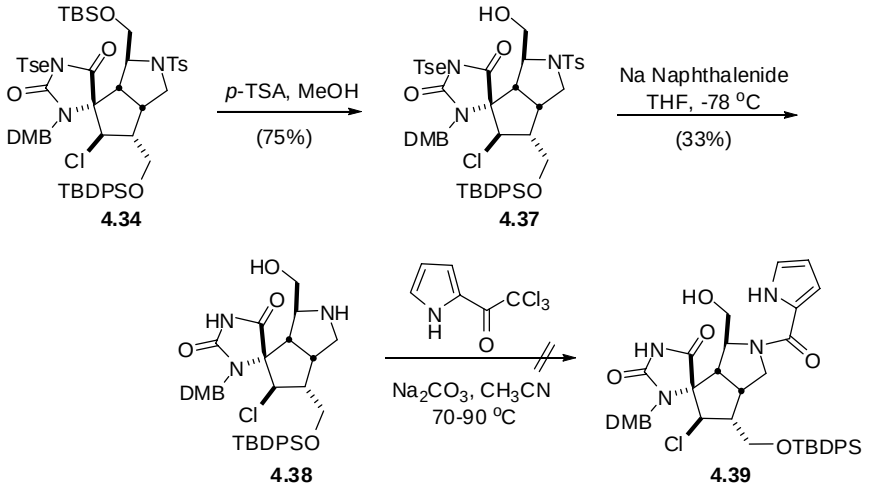
TBS reprotection of alcohol **4.23** gave TBS-silyl ether **4.30**, which was subjected to the following three-step deoxygenation sequence to give protected pyrrolidine **4.33** in high yield (Scheme 40). The oxidation/chlorination reactions also worked well on Ts-pyrrolidine **4.33** to give chlorocyclopentane **4.34** in 60% yield, after which both Ts and Tse were removed using sodium naphthalenide to give pyrrolidine **4.35**. Disappointingly, attempts to acetylate pyrrolidine **4.35** with 2-trichloroacetyl pyrrole failed to give the desired product **4.36**.

Scheme 40



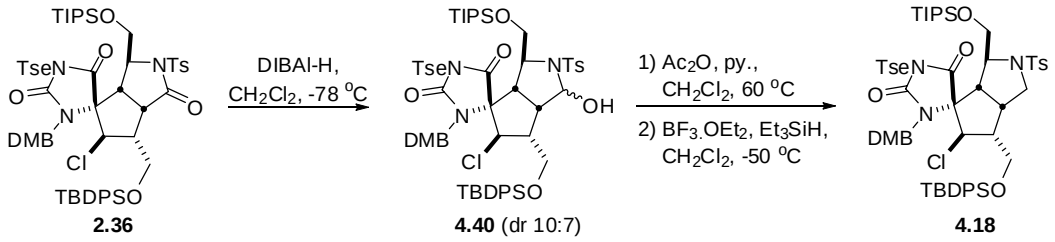
After unsuccessful acylation attempts on TBS-protected pyrrolidinol **4.35**, pyrrolidinol **4.38** was prepared via selective deprotection of TBS and detosylation from **4.34** (Scheme 41). However, the following attempts to acylate the pyrrolidine nitrogen, without any steric hindrance from the pendant alcohol protecting group, were still unsuccessful, even under harsh microwave conditions. The unexpected reactivity of pyrrolidinol **4.38** raised questions about its true indentity, and also those of **4.34** and **4.18**. A different synthetic route to reach pyrrolidine **4.18** was planned to corroborate the presumably identical compound synthesized previously (Scheme 35).

Scheme 41



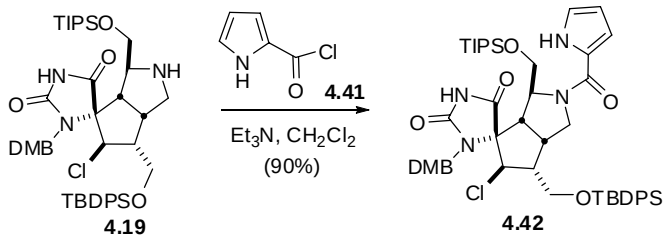
Ts-protected pyrrolidine **4.18** was obtained via selective reduction of the lactam carbonyl in chlorocyclopentane **2.36**, followed by acetylation and reduction (Scheme 42). This verified the identity of **4.18** obtained previously. Notably, two diastereomers of alcohol **4.40** were observed (dr 10:7), contrary to previous cases, i.e., the reduction of tricycles **2.34**, **4.23** and **4.30**, where only one diastereomer of the resulting alcohol was observed. This is due to the fact that in spirocycle **2.36**, the α-face of lactam carbonyl is not totally blocked by the bulky TBDPS, allowing reduction from both faces.

Scheme 42



Eventually the pyrrole-acylation was achieved when pyrrole-2-carbonyl chloride (**4.41**) was used as the coupling partner. After conversion of the commercially available pyrrole-2-carboxylic acid to acid chloride **4.41**,[61] pyrrolidine **4.19** was successfully acylated with the pyrrole-2-carbonyl chloride, generating the desired product **4.42** in high yield (Scheme 43).

Scheme 43

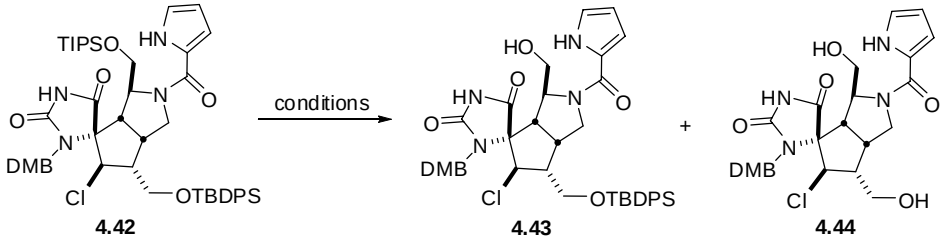


C. Synthesis of an Advanced Pentacyclic Intermediate

Attempts on selective removal of TIPS over TBDPS from tetracycle **4.42** using TBAF at low temperature (Table 3, entry 1) resulted in no reaction. At ambient temperature, non-selective desilylation was observed, giving 22% yield of desired product **4.43** and 78% yield of diol **4.44** (entry 2). Presence of excess amount of AcOH totally deactivated TBAF and no reaction was observed even at ambient temperature, while use of 0.2 equivalents of AcOH slightly enhanced the selectivity of the desilylation (entry 4). Finally, selective TIPS removal was achieved under acidic conditions using *p*TSA. With proper control of reaction time (around 18 h), the desired

alcohol **4.43** could be isolated in 82% yield. Longer reaction time led to the formation of diol **4.44**.

Table 3. Selective removal of TIPS over TBDPS



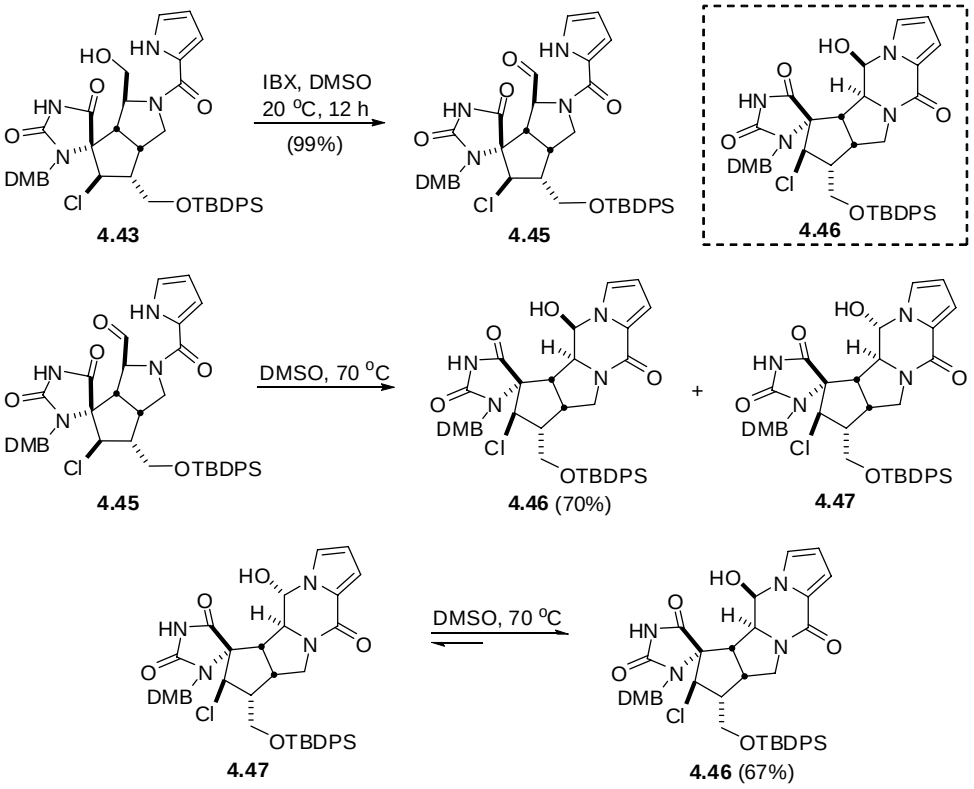
4.42 **4.43** **4.44**

entry	conditions	results
1	TBAF, THF, -50-0 °C	no reaction
2	TBAF, THF, 20 °C	22% **4.43**, 78% **4.44**
3	TBAF, AcOH (5 eq.), THF, 20 °C	no reaction
4	TBAF, AcOH (0.2 eq.), THF, 20 °C	31% **4.43**, 69% **4.44**
5	*p*TSA, MeOH, 20 °C, 18 h	82% **4.43**

According to literature precedent on a simplified system,[62] IBX oxidation of alcohol **4.43** was projected to give aminal **4.46** directly as a result of *in situ* cyclization of the pyrrole nitrogen onto the aldehyde formed from oxidation. However, subjecting alcohol **4.43** to IBX oxidation gave aldehyde **4.45** as the only product (Scheme 44). Attempts to cyclize the pyrrole onto the aldehyde intramolecularly failed under various heating conditions and Lewis acid mediated conditions. Eventually, heating pure aldehyde **4.45** in DMSO to 70 °C provided the desired product **4.46** in 70% yield along with a small amount of the diastereomeric aminal **4.47**. *N,O*-Hemiaminal **4.46** could be separated from its diastereomer **4.47** via column chromatography. The purified aminal

4.47 could be equilibrated back to the desired diastereomer **4.46** under thermodynamic conditions.

Scheme 44



The stereochemistry of the hemiaminal carbon (C6, Figure 13) in **4.46** was determined by two factors: coupling constants and 1D NOESY correlations. In an analogous but much simpler system,[62] the coupling constant between the aminal proton (with β-OH on the aminal carbon) and its vicinal proton was reported to be 2.6 Hz. This coupling constant corresponds to the H6-H10 coupling constant in hemiaminal **4.46** (Figure 13), which was found to be 3.0 Hz. These similar values suggest that the C6

hydroxyl group is in the β-face. This stereochemical assignment was confirmed undoubtedly by 1D NOESY NMR data. By irradiating aminal proton H6, nOe correlations were observed at the hydroxyl proton, vicinal proton H10 and neighboring pyrrole proton H5, meaning that H6 is in a *syn* relationship with vicinal proton H10. The relative stereochemistry of the central cyclopentane ring system, i.e., C11, C12, C16, C17 and C18 was also confirmed by NOESY correlations as shown in Figure 13.

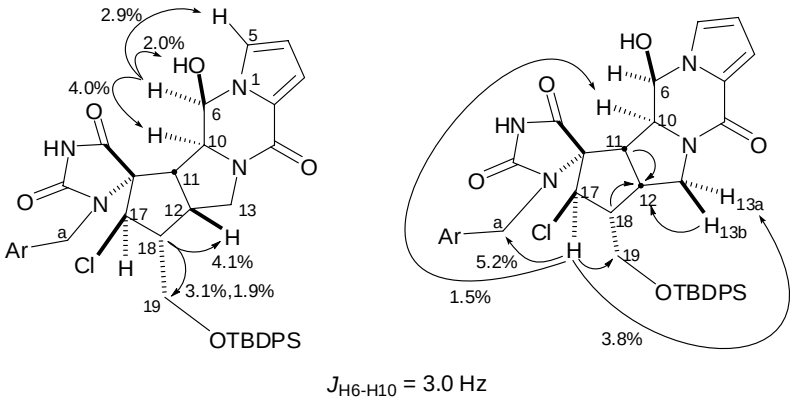
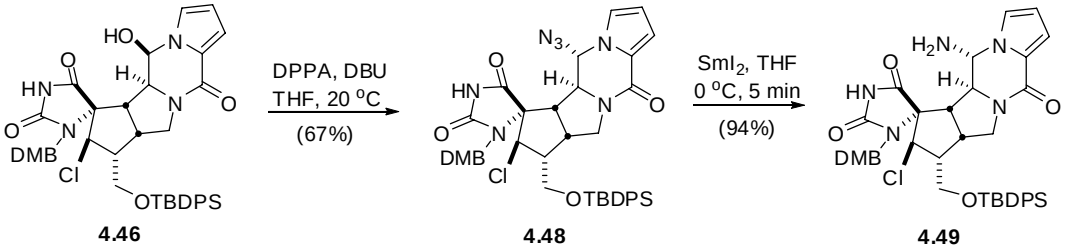


Figure 13. 1D NOESY data of *N,O*-hemiaminal **4.46**

Conversion of the hydroxyl group in hemiaminal **4.46** to an amine functionality (**4.49**) was accomplished by Mitsunobu type azidation[63] and subsequent azide reduction by samarium diiodide[64] (Scheme 45). The stereochemistry of C6 center was inverted during the azidation step, leading to the α-NH_2 in *N,N*-hemiaminal **4.49**. This stereochemical outcome was confirmed by coupling constant analysis and 1D NOESY NMR data (Figure 14).

Scheme 45



The observed coupling constant of 10.0 Hz between H6 and H10 (Figure 14) in **4.49** was consistent with the literature value of 9.7 Hz for a related system,[62] indicating an *anti* relationship between H6 and H10. Therefore the amino group was determined to be α-NH_2 at the aminal carbon C6. 1D NOESY data revealed correlation between proton H6 and adjacent bridgehead proton H11, but no correlation between H6 and vicinal proton H10. In contrast, before the azide formation, NOESY data of aminal **4.46** showed strong nOe correlation between H6 and H10 (Figure 13). This result further verified the stereochemistry of the hemiaminal carbon center C6.

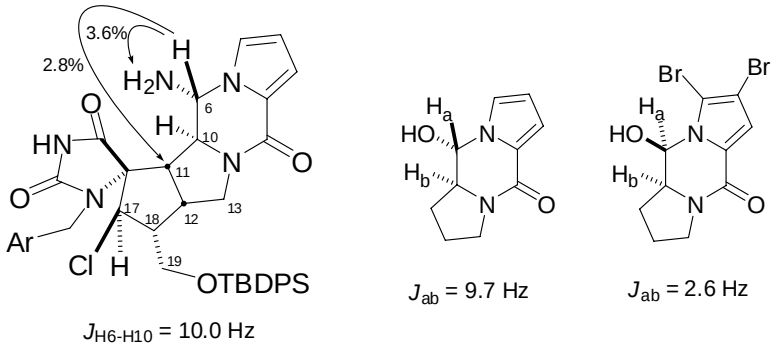
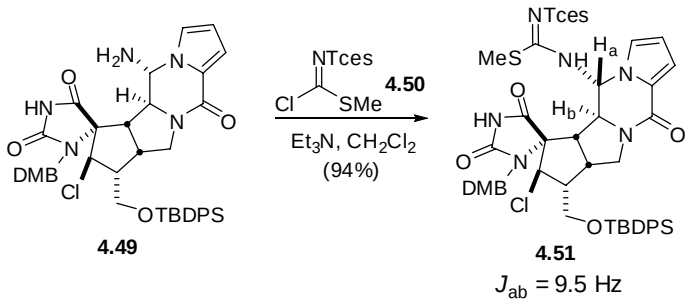


Figure 14. 1D NOESY data of *N,N*-hemiaminal **4.49**

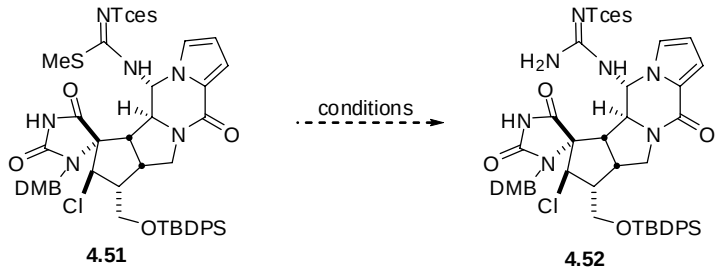
The original plan to access the final ring system in epi-palau'amine (Scheme 30) involves a C-H amination strategy based on Du Bois's Rh(II)-catalyzed C-H insertion reactions.[65] To this end, a Tces-protected guanidine needed to be installed onto the amino group in pentacycle **4.49**. An isothiourea functionality was installed first with imidoyl chloride **4.50**[65] to give isothiourea **4.51** (Scheme 46). The coupling constant of the aminal proton (Ha as shown in Scheme 46) with its vicinal proton was 9.5 Hz, consistent with the corresponding coupling constant observed in intermediate **4.49**.

Scheme 46



However, removal of the thiomethyl group to generate guanidine **4.52** was problematic. A brief study on this reaction did not meet with success (Table 4). When the substrate **4.51** was treated with mercury dichloride and hexamethyldisilazane (HMDS),[65] a complex mixture of unidentified products was observed. Use of ammonia[66] only resulted in recovery of *N*,*N*-hemiaminal precursor **4.49**. Other possible ways to effect this conversion remains to be explored.

Table 4. Attempts on conversion of isothiourea **4.51** to guanidine **4.52**



4.51 **4.52**

entry	conditions	results
1	$HgCl_2$, HMDS, THF, 20 °C	multiple products
2	NH_3 (xs), MeOH, 20 °C	**4.49** (100%)
3	NH_3 (1.0 eq.), MeOH, 20 °C	**4.49**[a]

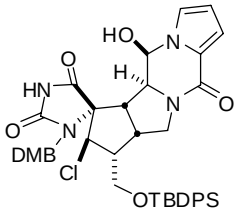
a: product verified by NMR; yield not determined

D. NMR Data Comparison with Palau'amine Isolation Data

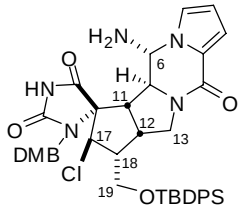
With the purpose of determining the C6 stereochemistry of *N,O*-hemiaminal **4.46** and verifying the structural assignment of the remainder part of the molecule, a thorough 1D NOESY NMR analysis was performed, as briefly discussed in the previous section. At the same time, coupling constants of some key protons on the central aza-bicyclo[3.3.0]octane system were also examined, and some significant discrepancies were discovered, as shown in Table 5. Two sets of coupling constants differ substantially from the originally reported values for the natural palau'amine. Protons H11 and H12 have a coupling constant of 14.1 Hz in the natural product, while the corresponding coupling constant in synthesized pentacycle **4.46** with the proposed *cis* aza-bicyclo[3.3.0]octane is 9.0 Hz. Protons H17 and H18 have a coupling constant of 7.9 Hz in the natural palau'amine, while the same set of protons have a 12.0 Hz coupling in

pentacycle **4.46** (Table 5). These findings raised doubts regarding the original structural assignments of palau'amine.

Table 5. Coupling constant comparison for palau'amine and pentacycles **4.46** and **4.49**



4.46



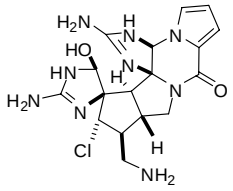
4.49

proton position (mult, *J* Hz)	palau'amine[10]	pentacycle **4.46**	pentacycle **4.49**
11	d, 14.1	dd, 5.5, 9.0	dd, 4.0, 9.0
12	dddd (14.6, 10.2, 9.0, 7.2)[36]	p, 9.0	p, 9.0
13α	dd, 10.4, 7.3	dd, 9.0, 12.5	dd, 8.0, 12.0
13β	dd, 10.3, 10.4	overlapped H_{10}	t, 12.0
17	d, 7.9	d, 12.0	d, 12.0
18	dddd (qd, 9.0, 5.0)[36]	m	m
19	dd, 13.2, 7.0	dd, 3.5, 11.0; dd, 7.5, 11.0	dd, 3.5, 11.0; dd, 7.5, 11.0

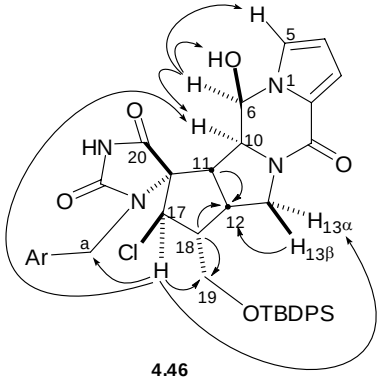
A close comparison of NOESY data with the original isolation report[10] also revealed a major discrepancy. For a *cis* fused aza-bicyclo[3.3.0]octane system, as in the originally proposed palau'amine structure, one would expect a strong nOe correlation between the two bridge head protons (H11 and H12). This was indeed observed in the advanced pentacycle **4.46** containing the *cis* fused aza-bicyclo[3.3.0]octane structural feature (Table 6), however, this important correlation was not reported in the isolation

paper. Since the ring fusion between the pyrrolidine and chlorocyclopentane ring systems in pentacycle **4.46** was obtained from a Diels-Alder cycloaddition, and with the NOESY data observed, it is evident that the two ring systems are *cis* fused. Hence these discrepancies discovered in coupling constant and nOe data suggested that the original palau'amine structural assignment could be incorrect.

Table 6. 1D NOESY correlation comparison for palau'amine and pentacycle **4.46**



1.46: revised structure of palau'amine



4.46

proton position	palau'amine[36]	pentacycle **4.46**
11	6, 13β, 18	12, 13β, 18
13β	13α, 11, 18	13α, 12
17	12, 19, 23	13α, 19
18	11, 13β	12, 19

Recently, palau'amine was reisolated,[36] along with the isolation of stylissadine A and B by Quinn and co-workers.[30] Reexamination of ROESY and coupling constant data warranted a structural revision of palau'amine and related congeners (*vide supra*, Chapter I). The comparison of selected nOe correlations are listed in Table 6. Besides

the bridge head protons H11-H12 correlation, other major differences include correlations between H13β-H11 (**1.46**), H13β -H12 (**4.46**), H17-H12 (**1.46**), H17-H13α (**4.46**), H18-H11 (**1.46**), H18-H13β (**1.46**) and H18-H12 (**4.46**). The observed ROESY data clearly support a *trans* fused aza-bicyclo[3.3.0]octane system and revised C17 stereochemistry.

E. Conclusion

Synthetic efforts toward the intended epi-chloro palau'amine (C17 epimer) suffered from substantial difficulties in the early stage pyrrole-acylation studies. Finally application of pyrrole-2-carbonyl chloride successfully installed the pyrrole moiety. Subsequent transformations afforded advanced pentacyclic intermediate **4.51**, possessing the whole carbon framework and all but one ring system of palau'amine. After reaching pentacycle **4.46**, thorough examination of coupling constants and NOESY NMR data revealed a few significant discrepancies with the original palau'amine NMR data. Coupled with recent structural revision of palau'amine, it was found that advanced pentacycle **4.51** for the initial target C17 epi-palau'amine now becomes an intermediate for C12 epi-palau'amine.

CHAPTER V

ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-PHAKELLIN AND (+)-MONOBROMOPHAKELLIN: A CONCISE PHAKELLIN ANNULATION STRATEGY FOR PALAU'AMINE SYNTHESIS

A. Introduction

The phakellins (**1.9-1.11**) belong to the pyrrole-imidazole family of marine alkaloids and are proposed to be derived biosynthetically from oroidin (**1.1**) and congeners (Figure 15).[7,8] This family of marine alkaloids has attracted interest from both the synthetic and biological perspectives, due to their intriguing structural features and, in some cases, potent biological activities (*vide supra*, Chapter I). The monomeric pyrrole-imidazole members (-)-dibromophakellin (**1.11**) and (-)-monobromophakellin (**1.10**) were initially isolated by Sharma and Burkholder in 1969 from the marine sponge *Phakellia flabellata*[15] and subsequently enantiomeric (+)-dibromophakellin (*ent*-**1.11**) was isolated from *Pseudoaxinyssa cantharella* in 1985.[16] Even though (+)-monobromophakellin (*ent*-**1.10**) and (+)-phakellin (*ent*-**1.9**) have not been reported as isolates from natural sources, it is reasonable to expect that these alkaloids could be existent in nature as well. The phakellstatins (**1.12, 1.13**) are related members of this family bearing a cyclic urea rather than a cyclic guanidine.[18] The dimeric oroidin alkaloids palau'amine (**1.46**) and related congeners contain a phakellin subunit within their structure.

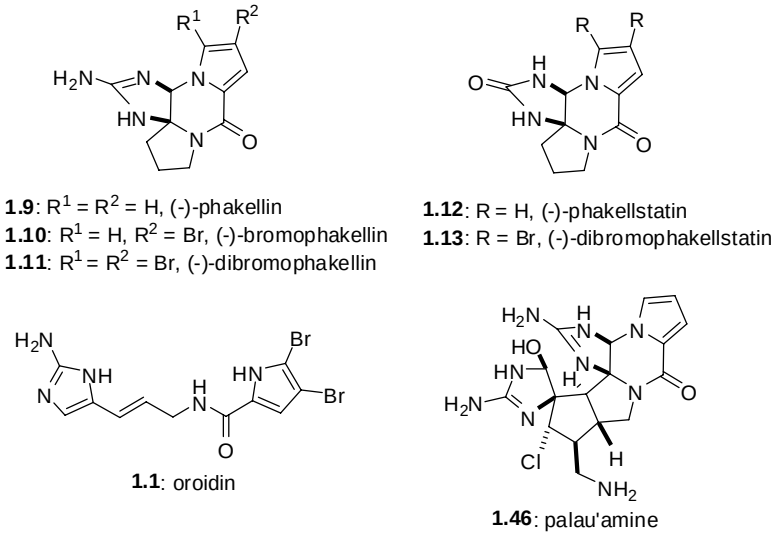
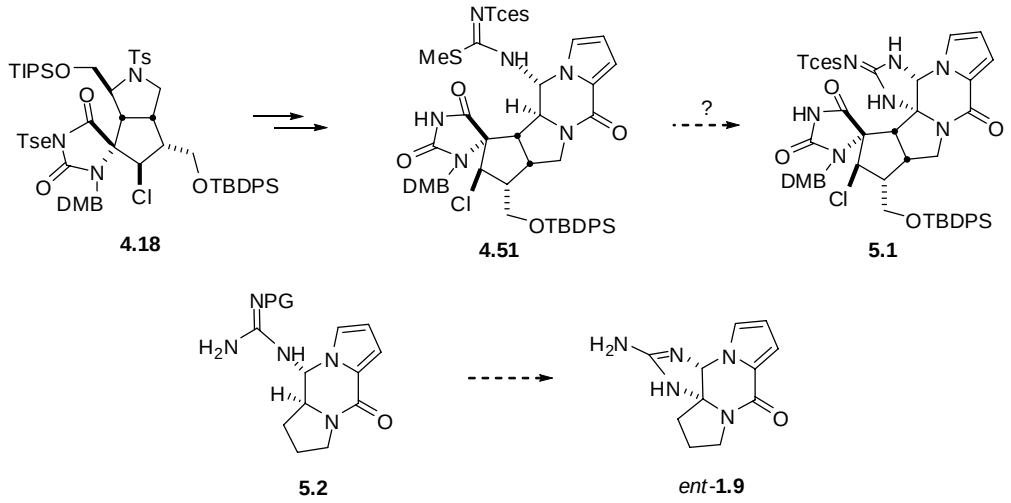


Figure 15. Structure of tetracyclic oroidin alkaloids phakellins and phakellstatins

The concise, biomimetic synthesis of *rac*-dibromophakellin reported by Büchi stands as a benchmark for syntheses of these alkaloids and most subsequent syntheses of phakellin have utilized related oxidative cyclization strategies.[67] All reported racemic syntheses of the dibromophakellstatin have also utilized related strategies.[68] We previously reported the enantioselective synthesis of (+)-dibromophakellstatin (*ent*-**1.13**) employing a Hoffman rearrangement to simultaneously introduce the second aminal center (C10) and cyclize the incipient isocyanate to deliver the cyclic urea.[69] In connection with our synthetic efforts toward epi-palau'amine, we have sought expedient strategies to annulate the phakellin substructure onto a cyclopentane core (**4.18**, Scheme 47). After an advanced pentacyclic intermediate **4.51** was synthesized, concerns regarding the projected C-H amination strategy (*vide infra*) to construct the final ring system granted necessity for a model study. Being a substructure of palau'amine,

phakellin would be a perfect model for this purpose. Studies on the cyclization of guanidine **5.2** would provide valuable information for palau'amine synthesis. In addition, the absence of an enantioselective phakellin synthesis in literature added further impetus to our synthetic efforts towards phakellins.

Scheme 47

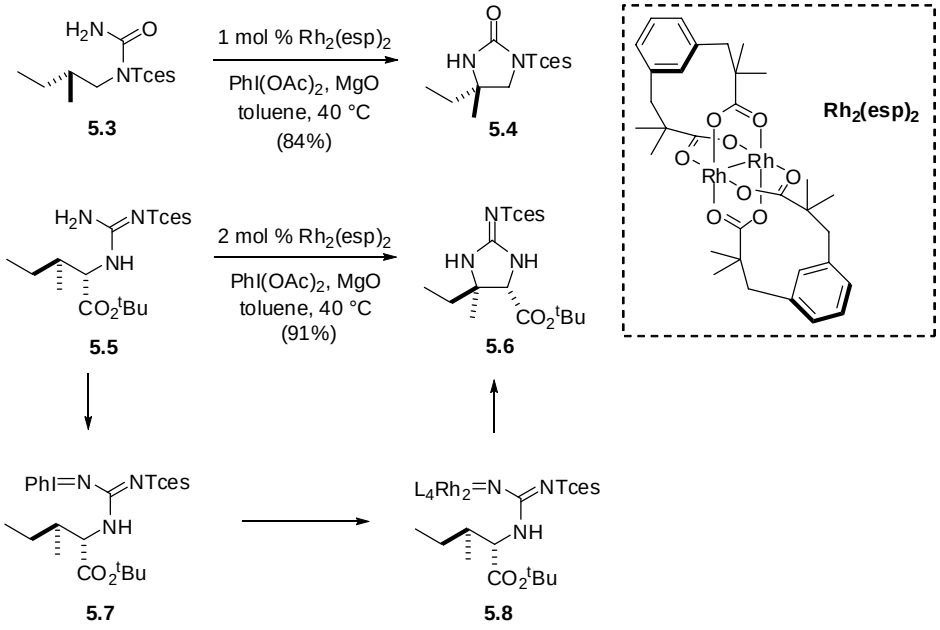


B. The C-H Amination Strategy

Direct methods for the amination of C-H bonds have become established tools for the assembly of nitrogen-based heterocycles and related amine derivatives.[70] Du Bois has reported catalytic, oxidative cyclizations of both primary carbamates and sulfamate esters to give the corresponding 5- and 6-membered ring products, respectively.[71] A recent advance in this field reported by the same group showed that stereospecific intramolecular cyclization of urea and guanidine derivatives via rhodium (II) catalyzed C-H amination gave cyclic ureas and guanidines in high yields (Scheme 48).[72] This

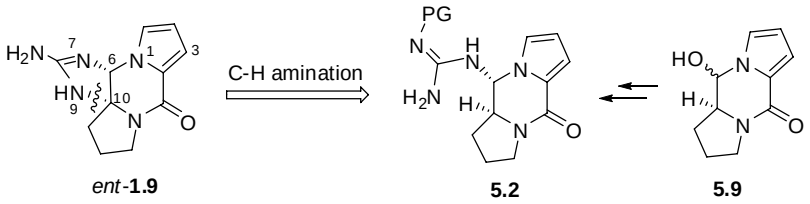
methodology is potentially very useful for the synthesis of cyclic urea/guanidine containing natural products, such as saxitoxin,[73] phakellstatins and phakellins.

Scheme 48



In our previous studies, we recognized the stability of C6 aminals in these tricyclic systems[74] and this led us to consider a strategy involving a key C-H amination disconnection (N9-C10, Scheme 49) towards phakellin, based on recent work by Du Bois,[72] employing guanidine **5.2** as a substrate accessible from the known aminal **5.9** derived from *L*-proline. This would enable a mild installation of the cyclic guanidine in a stereospecific fashion toward phakellins and would also be applicable towards more functionalized substrates leading to palau'amine.

Scheme 49

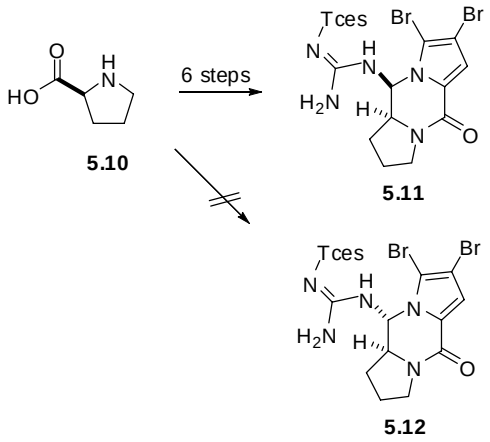


ent-**1.9** **5.2** **5.9**

1. Synthesis of the C-H Amination Precursor

Initially, we set out to synthesize a guanidine substrate **5.12** with a prerequisite of obtaining the required *cis*-arrangement between the guanidine and vicinal C-H bond for subsequent intramolecular amination (Scheme 50). Unfortunately, this goal could not be reached due to an unexpected epimerization during the 6-step synthetic sequence from (*L*)-proline **5.10**, leading to the diastereomeric guanidine **5.11**, which was not suitable for intramolecular C-H amination.[75]

Scheme 50

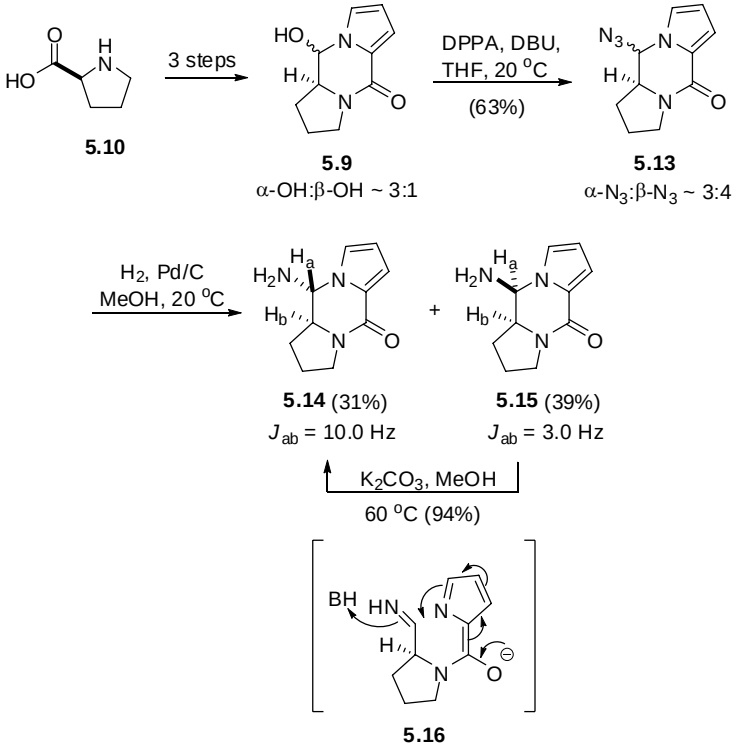


5.10 **5.11** **5.12**

In an alternative approach to make a guanidine substrate with the required stereochemistry, (*L*)-Proline **5.10** was converted to the known hydroxydipyrrolopyrazinone **5.9** in three steps as an inseparable and inconsequential (*vide infra*) mixture of diastereomers, with a ratio of α-OH:β-OH ~ 3:1 (Scheme 51).[76,62] Carbinolamines **5.9** were converted to aminals **5.14**/**5.15** by azidation with diphenylphosphoryl azide and subsequent reduction by hydrogenolysis. Notably, azide **5.13** was obtained as an inseparable mixture of diastereomers, however, with a different diastereomeric ratio: α-N_3:β-N_3 ~ 3:4. Starting from carbinolamines **5.9** with a 3:1 dr (α-OH:β-OH), one would expect a dr of 1:3 (α-N_3:β-N_3) for the azide products **5.13** after a Mitsunobu type azidation process. The ratio of 3:4 for α-N_3:β-N_3 suggested that epimerization happened during the azidation to yield more thermodynamically favored α-N_3 product. Fortunately, after the azide reduction, the diastereomeric aminals **5.14**/**5.15** (dr ~3:4) could be separated by flash chromatography. They displayed a large and a small coupling constant between aminal proton and vicinal proton (J_{ab} = 10.0 Hz and 3.0 Hz), respectively.[62]

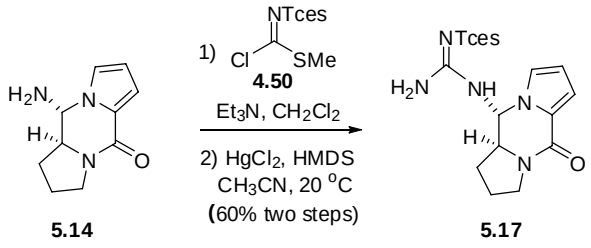
Based on the speculation that the α-N_3 diastereomer is thermodynamically favored over the β-N_3 (*vide supra*), we attempted to convert β-NH_2 aminal **5.15** to the thermodynamically favored α-NH_2 aminal **5.14** by warming in methanol under weakly basic conditions (Scheme 51). This indeed provided the epimerized product **5.14** in 94% yield, presumably *via* a ring-opened imine intermediate **5.16**.

Scheme 51



With an efficient route to the required *anti*-substituted pyrazinone **5.14** in hand for the projected C-H amination, the trichloroethoxysulfonyl (Tces)-protected guanidine **5.17** was synthesized in two steps via formation of an isothiourea intermediate and subsequent conversion of the isothiourea to guanidine **5.17** (Scheme 52).[72]

Scheme 52



The Tces-protected guanidine **5.17** was carefully crystallized via slow evaporation of its EtOH solution. The resulting crystals were subjected to X-ray analysis and found to be co-crystals of the guanidine **5.17** and EtOH. X-ray structure of guanidine **5.17** confirmed its identity and stereochemistry at the aminal carbon center C6 (C(1A) in Figure 16).

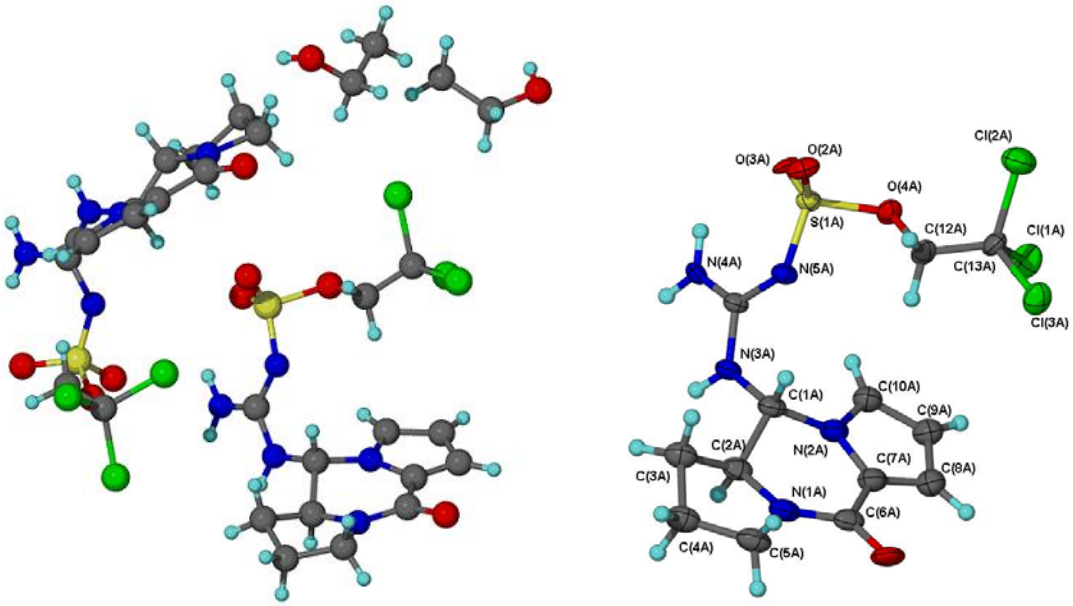


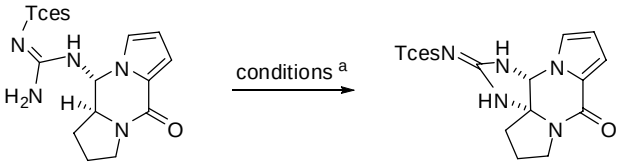
Figure 16. Crystal structure of guanidine **5.17** by X-ray crystallography

2. C-H Amination Studies

With guanidine **5.17** in hand, we next studied the C-H amination process employing conditions reported by Du Bois.[72] However, reactions using $Rh_2(esp)_2$ catalyst (Scheme 48) did not give any promising results (Table 7, entry 1-3). It was

reasoned that the esp ligands on rhodium (II) are too bulky and therefore hamper the Rh-nitrene species from approaching the tertiary C-H reaction center. Switching to a less bulky rhodium catalyst, i.e. $Rh_2(OAc)_4$, did not provide any desired product either (Table 7, entry 4-5). After some experimentation, we found that Tces-protected phakellin **5.18** could indeed be obtained in relatively low yield employing $Rh_2(OTFA)_4$ as catalyst and CH_2Cl_2 as solvent under conventional heating or microwave heating conditions (Table 1, entry 6-7). CH_2Cl_2 proved to be a better solvent for this reaction compared with aromatic solvent such as benzene, toluene or benzotrifluoride[77] (BTF).

Table 7. Studies on C-H amination of guanidine **5.17**



5.17 **5.18**

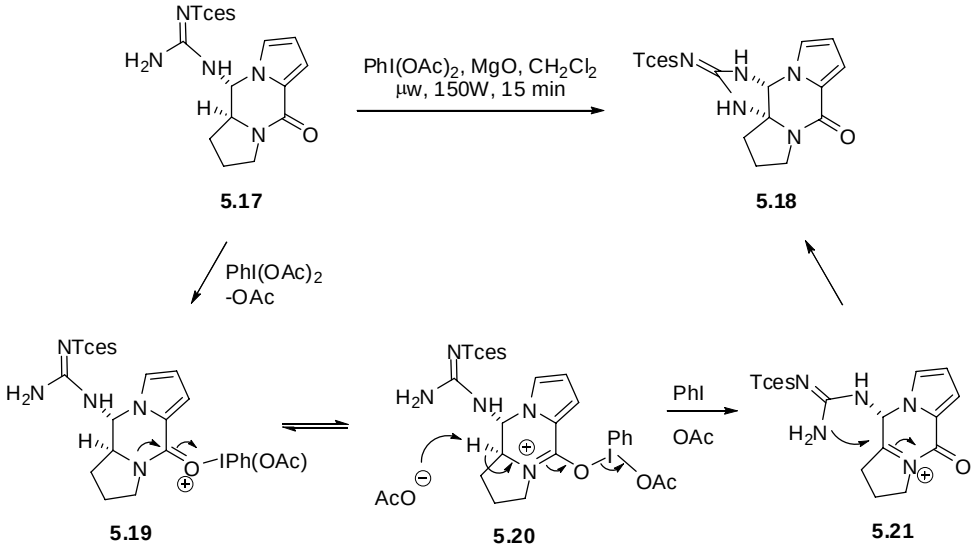
entry	catalyst	solvent	heating conditions	results
1	$Rh_2(esp)_2$	toluene	40 °C	recovered **5.17**
2	$Rh_2(esp)_2$	CH_2Cl_2	40 °C	degradation
3	$Rh_2(esp)_2$	BTF[b]	45 °C	recovered **5.17**
4	$Rh_2(OAc)_4$	BTF	70 °C	recovered **5.17**
5	$Rh_2(OAc)_4$	CH_2Cl_2	70 °C	partial rcvd **5.17**[c]
6	$Rh_2(O_2CCF_3)_4$	CH_2Cl_2	60 °C, 24 h	**5.18** (30%)[d]
7	$Rh_2(O_2CCF_3)_4$	CH_2Cl_2	μw, 150W, 5 min	**5.18** (31%)[d]
8	$Rh_2(O_2CCF_3)_4$	BTF	μw, 200W, 10 min	recovered **5.17**
9	$Rh_2(O_2CCF_3)_4$	benzene	μw, 150W, 15 min	**5.18** (<10%)

Note: (a) Rhodium (II) catalyst, 2-3 equiv. $PhI(OAc)_2$, 3 equiv. MgO, solvent; (b) benzotrifluoride, or α,α,α-trifluorotoluene; (c) partial decomposition; d) with 40-48% starting material recovery.

C. The Oxidative Cyclization Pathway

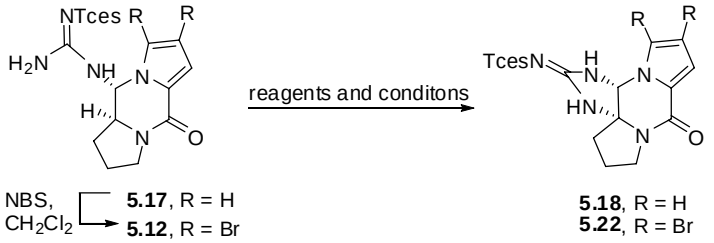
In order to better understand the C-H amination reaction so that proper conditions could be derived for improving the yield, a control experiment was tested without the use of any rhodium (II) catalyst. Interestingly, this experiment revealed that the rhodium (II) catalyst was not required for the formation of desired cyclized guanidine **5.18** (Scheme 53). This result suggested that rather than a C-H amination process, a simple oxidative cyclization mechanism might be operative, in which an acyliminium[78] intermediate **5.21** was formed upon oxidation of the pyrazinone moiety in guanidine **5.17** by iodobenzenediacetate, and subsequent cyclization of the pendent guanidine onto the iminium gave the desired cyclic guanidine **5.18**.

Scheme 53



1. Optimizing the Reaction Conditions

Table 8. Screening of the oxidative cyclization conditions



entry	oxidant	solvent	heating conditions	results
1	$PhI(OAc)_2$, MgO	CH_3CN	μw, 150W, 10 min	**5.18** (38%)
2	$PhI(OAc)_2$, MgO	Tol./CH_3CN	μw, 150W, 20 min	**5.18**[a]
3	$PhI(OAc)_2$	CH_3CN	65 °C	**5.18** (40%)[b]
4	$PhI(OAc)_2$, Et_3N	CH_3CN	20-50 °C	no **5.18**[c]
5	$PhI(O_2CCF_3)_2$	CH_3CN	50 °C	degradation
6	IBX	DMSO	60 °C	no reaction
7	CAN	CH_3CN/H_2O	20 °C	unidentified pdt[d]
8	$Cu(OAc)_2$	CH_3CN	20-65 °C	no reaction
9	$PhI(OAc)_2$	CH_3CN	μw, 150W, 10 min[e]	trace **5.22**

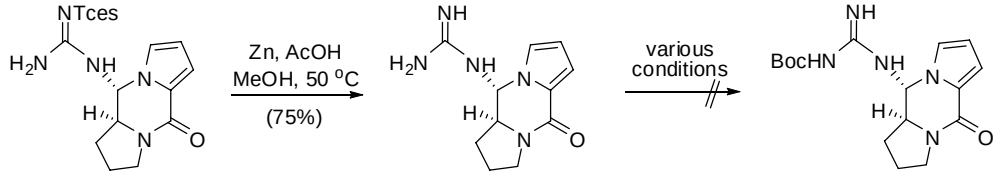
Note: (a) cleaner reaction, but still low yield; (b) conversion determined by NMR; (c) partially recovered **5.17**; (d) cude NMR showed it was the pyrrole-oxidized product; (e) **5.12** was used.

Attempts to optimize this oxidative cyclization process by changing solvents and reaction temperature (Table 8), did not lead to further improvements in yield and while complete conversion of starting materials was typically observed, the cyclized product was always accompanied by very polar decomposition products. Several other oxidants previously reported for amide oxidations to acyliminium species including 2-iodoxybenzoic acid (IBX)[79], cerium (IV) ammonium nitrate (CAN)[80], and copper (II)[81] salts were investigated, however these resulted in either no reaction or primarily decomposition. Among the various oxidants and heating conditions studied, the initially

employed iodonium benzenediacetate in combination with MgO under microwave condition gave the highest yields of Tces-phakellin **5.18** (30-38%). While this reaction could be scaled up to 100 mg, a drop of yield to ~20% was observed. Considering that the pyrrole is known to be susceptible to oxidation, we also studied the oxidative cyclization of dibrominated guanidine **5.12**, in hope that the dibrominated pyrrole should be less prone to oxidation and therefore render less side products and higher yield of the desired product. Disappointingly, this only led to trace amount of Tces-protected dibromophakellin **5.22**, with mainly decomposition of the starting material (Table 8, entry 9).

2. Studies on Different Protecting Groups

Scheme 54

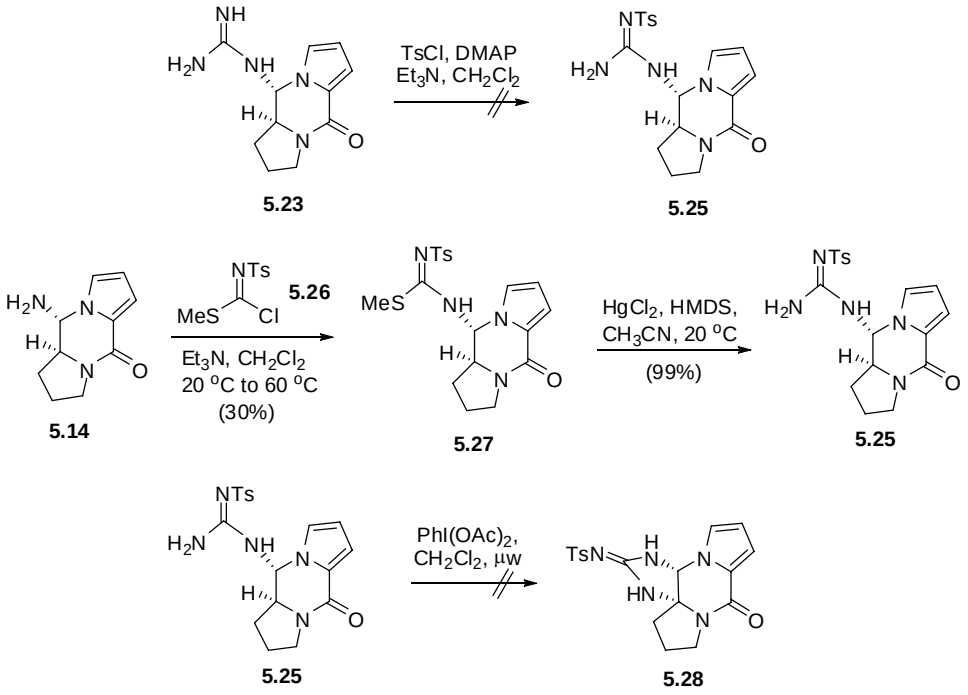


5.17 **5.23** **5.24**

According to the mechanistic speculation, a less electron-withdrawing protecting group on the pendent guanidine would improve the yield of the oxidative cyclization. Boc protecting group, which is a very mild electron withdrawing group compared with 2,2,2-trichloroethoxysulfonyl (Tces), was studied initially for this purpose. Removal of the Tces group from guanidine **5.17** gave free guanidine **5.23** in good yield (Scheme 54).

Unfortunately, after unsuccessful attempts on installing the Boc group onto guanidine **5.23** under various conditions, this route was abandoned.

Scheme 55



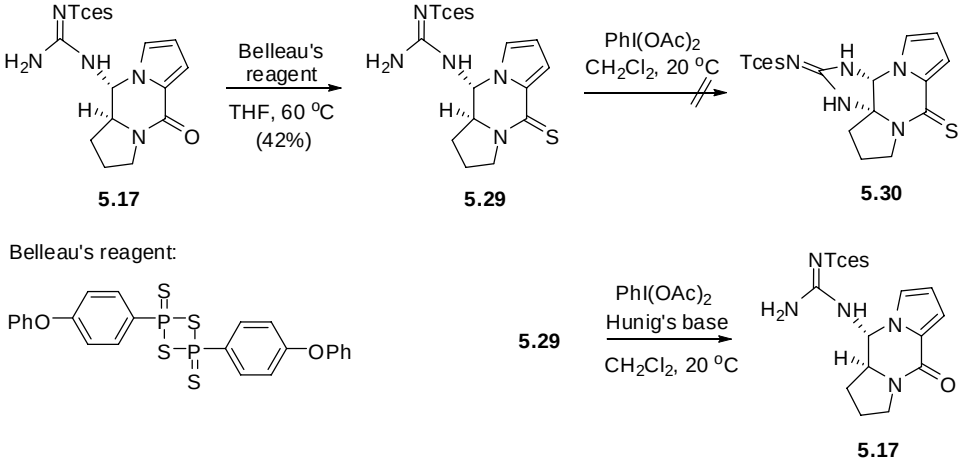
The corresponding Ts-protected guanidine **5.25** was also studied (Scheme 55). Initial efforts to convert free guanidine **5.23** to Ts-guanidine **5.25** did not meet with success, so we turned to a route analogous to the one used for synthesis of Tces-guanidine **5.17**. Starting from amine **5.14**, the isothiourea functionality was installed using imidoylchloride **5.26**, which was obtained following known procedure[72] from commercially available *N*-[bis(methylthio)methylene]-*p*-toluenesulfonamide. The following desulfuration of isothiourea **5.27** yielded Ts-guanidine **5.25**. Disappointingly,

subjecting Ts-guanidine **5.25** to oxidative cyclization did not yield Ts-protected phakellin **5.28** under identical conditions, resulting in extensive degradation of the material.

3. Studies on Piperazine-thione and Urea Substrates

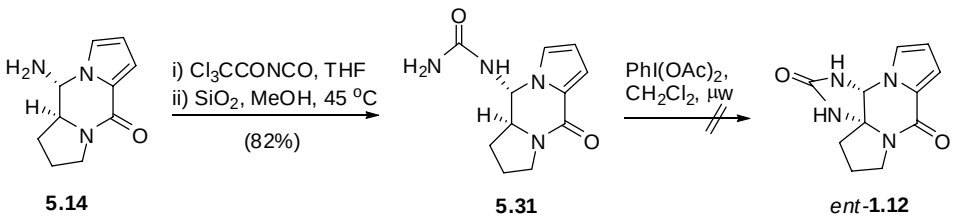
In another effort to improve the oxidative cyclization reaction, we sought to explore the utility of the thio-version of guanidine **5.17**, i.e. piperazine-thione **5.29** (Scheme 56), based on the reasoning that a thio-carbonyl is more nucleophilic than the amide carbonyl in piperazinone **5.17** and can be oxidized more easily with iodonium type oxidants.[82] This would make the oxidation more chemoselective and give better yield of the desired product.

Scheme 56



Conversion of the amide carbonyl to a thiocarbonyl was achieved by using Belleau's reagent.[83] However, the piperazine-thione **5.29** was not stable in the presence of oxidant $PhI(OAc)_2$ and decomposed rapidly into very polar materials. Adding Hunig's base (diisopropylethylamine) to the reaction, according to literature example on a similar type of reaction,[68d] helped to prevent the rapid decomposition of the starting material **5.29**, but the major product observed was the piperazinone **5.17**.

Scheme 57

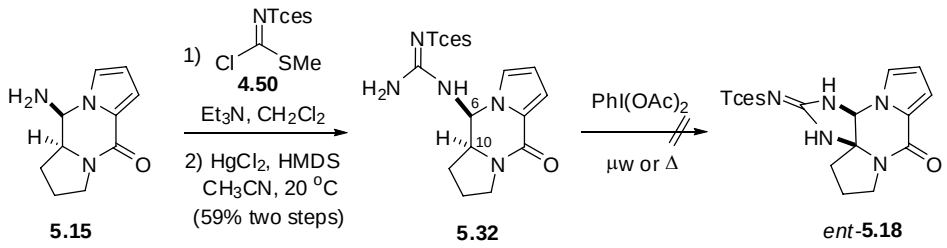


Based on the results obtained from oxidative cyclization reactions, we envisioned that urea **5.31** would be worth studying for the synthesis of (+)-phakellstatin (*ent*-**1.12**, Scheme 57). This would provide a very efficient synthetic pathway for (+)-phakellstatin and (+)-dibromophakellstatin. Urea **5.31** could be obtained from amine **5.14** by reaction with trichloroacetyl isocyanate and subsequent cleavage of the trichloroacetyl group. Unfortunately, the oxidative cyclization did not work on this substrate, instead generating a complex reaction mixture and no signs of the desired phakellstatin **1.12** were observed from NMR data.

4. Mechanistic Speculation

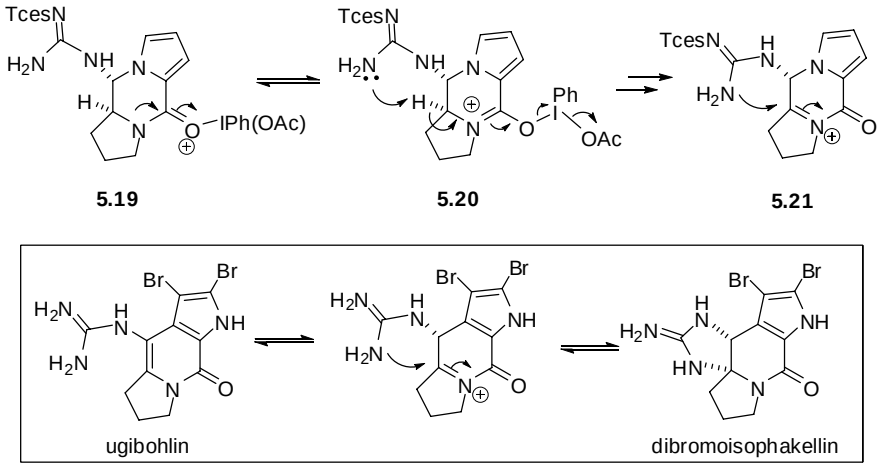
As proposed previously, one possible mechanistic scenario of the oxidative cyclization involves trapping of an acyliminium **5.21**, generated by oxidation of the vinylogous urea **5.17** with $PhI(OAc)_2$, by the pendant guanidine (Scheme 53). If this pathway was valid, we would expected that C6 diastereomer of Tces-guanidine **5.17** (**5.32**, Scheme 58) would give the opposite enantiomer of the cyclized product **5.18** (*ent*-**5.18**), regardless of the stereochemistry at C10.

Scheme 58



Guanidine **5.32** was easily accessed from amine **5.15**, C6 diastereomer of amine **5.14**, via the two-step procedure mentioned before. Interestingly, under the same oxidative conditions, the diastereomeric guanidine **5.32** did not provide Tces-protected (-)-phakellin. This result may point to the necessity of an intramolecular deprotonation by the pendant guanidine (Scheme 59), instead of intermolecular deprotonation. This mode of cyclization proceeding through an acyl iminium species is reminiscent of intermediates proposed by Al-Mourabit for interconversion of dibromoisophakellin and ugibohlin (Scheme 59, inset).[84]

Scheme 59



D. Synthesis of (+)-Phakellin and (+)-Monobromophakellin

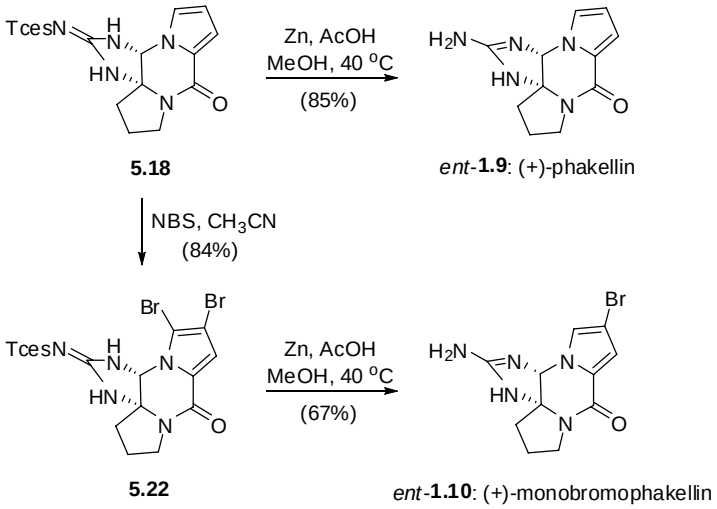
Removal of the 2,2,2-trichloroethoxysulfonyl group from *N*-Tces-phakellin **5.18** under reductive conditions (Scheme 60) afforded (+)-phakellin (*ent*-**1.9**) after purification by preparative, reverse phase HPLC. The synthetic material exhibited spectral data that correlated well with the reported data (Table 9).[16]

Table 9. Comparison of synthetic (+)-phakellin data and literature data

(+)-phakellin	reported[16]	synthetic
^{1}H-NMR (CD_3OD, ppm)	400 MHz: 8.54 (3H), 7.18 (1H), 6.90 (1H), 6.40 (1H), 6.12 (1H), 3.82(1H), 3.71 (1H), 2.39 (2H), 2.22 (2H)	500 MHz: 7.15 (1H), 6.93 (1H), 6.41 (1H), 6.08 (1H), 3.82 (1H), 3.68 (1H), 2.42 (2H), 2.22 (2H) [a]
IR (cm^{-1})	(KBr): 1680, 1580, 1390	(thin film): 1697, 1552, 1383
$[\alpha]_D$	+5 (0.81, CH_3OH)	+5.6 (0.90, CH_3OH)
MS	(EI) M^+: 231	(ESI) $M+H^+$: 232.1191 (calc. 232.1198)

a: NH_2 and NH peak not seen due to relative large amount of H_2O

Scheme 60



Bromination of *N*-Tces-phakellin **5.18** with NBS cleanly provided *N*-Tces-dibromophakellin **5.22**. Subsequent reduction with zinc in acidic methanol gave (+)-monobromophakellin (*ent*-**1.10**) resulting from cleavage of the Tces group and selective cleavage of the C5-bromo substituent.[85] Attempts to remove Tces group selectively using SmI_2 was unsuccessful, leading to the same result mentioned above. The spectral and optical rotation data for our synthetic material correlated well with published data for (-)-monobromophakellin (hydrochloride salt) (synthetic *ent*-**1.10**: $[\alpha]_D$ +112.5; literature[15] **1.10**: $[\alpha]_D$ -123) with the exception of the sign of rotation. Since there is no data reported in literature for (+)-monobromophakellin, a comparison of spectral data was done with the enantiomeric (-)-monobromophakellin[15] (Table 10).

Table 10. Comparison of synthetic (+)-monobromophakellin data and literature data

(+)-monobromo-phakellin·HCl	reported [a]	synthetic
^{1}H-NMR (DMSO-d_6, ppm)	9.87 (2H), 8.52 (2H), 7.46 (1H), 6.80 (1H), 6.08 (1H), ...(1H) [b], 3.50 (1H), 2.13-2.50 (2H), 2.06 (2H)	9.94 (2H), 8.49 (2H), 7.46 (1H), 6.79 (1H), 6.05 (1H), 3.63 (1H), 3.54 (1H) [c], 2.15-2.40 (2H), 2.01-2.08 (2H)
$[\alpha]_D$	-123 (3.015, CH_3OH)	+112.5 (0.10, CH_3OH)
IR (cm^{-1}) [d]	(KBr): 3300, 1650, 1590, 1480, 1420, 932, 618	(thin film): 3284, 1640, 1575 1481, 1421, 927, 610
MS	(EI) M^+: 309	(ESI) $M+H^+$: 310.0302 (calc. 310.0303)

a: (-)-monobromophakellin hydrochloride: Sharma, G.; Magdoff-Fairchild, B. *J. Org. Chem.* **1977**, *42*, 4118.
b: value in the reference was 6.35, which apparently was a mistake.
c: the peak partially overlapped with water peak.
d: free base without hydrochloride

E. Conclusion

The first enantioselective total synthesis of two members of the phakellin family of pyrroloimidazole alkaloids, i.e. (+)-phakellin and (+)-monobromophakellin, has been accomplished. The synthesis relies on a unique oxidative cyclization from a chiral tricyclic guanidine precursor (**5.17**) and results in a highly concise, enantioselective route to these targets (9 steps to (+)-phakellin; 10 steps to (+)-monobromophakellin from commercially available (*L*)-proline). The synthesis was 6 steps (7 steps for *ent*-**1.10**) in total from the known intermediate **5.9**, with the overall yield of ~10%, averaging 68% yield per step. Since the oxidative cyclization was a stereospecific process, the optical antipodes of these alkaloids would be accessible using (*D*)-proline as starting material. Importantly, this annulation process is a valuable contribution to palau'amine synthetic efforts as it provides an expedient annulation strategy onto cyclopentane precursors.

CHAPTER VI

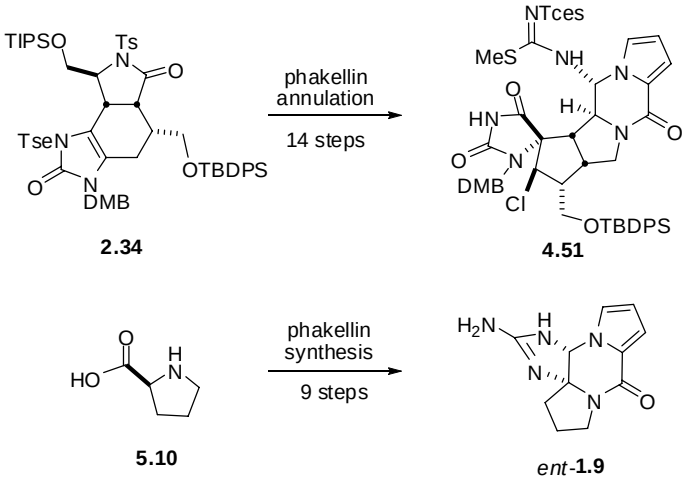
STUDIES TOWARD THE REVISED STRUCTURE OF PALAU'AMINE AND A UNIFIED STRATEGY TOWARD THE PALAU'AMINES AND AXINELLAMINES

A. Introduction

We proposed an approach to the originally accepted structures of palau'amine and axinellamine that involved a common synthetic intermediate derived from a Diels-Alder reaction (Chapter III, Scheme 15). The projected routes then diverged to address the difference in stereochemistry of the substituents on the central chlorocyclopentane ring systems of palau'amine and axinellamine. An intermolecular chlorination followed by selective epimerization at C12 would provide an intermediate with the required stereochemistry for axinellamine, while an intramolecular chlorination would give us access to the previously accepted *cis* azabicyclo[3.3.0]octane core structure of palau'amine. Disappointingly, our endeavors to realize the proposed intramolecular chlorination of the Diels-Alder adduct met with no success, and we opted instead to pursue the synthesis of epi-chloro palau'amine (Chapter IV, Scheme 30). This C17 epimer of palau'amine (**4.3**) features an inverted stereochemistry at the chlorine bearing carbon center, which could easily be accessed through an intermolecular chlorination pathway. An advanced pentacyclic intermediate (**4.51**) was accessed in 14 steps from the Diels-Alder adduct **2.34**, setting the stage for the projected C-H amination to construct the final ring system of palau'amine (Scheme 61). To test this strategy, the first

enantioselective synthesis of (+)-phakellin (*ent*-**1.9**) was pursued, as it would provide valuable information for palau'amine synthesis. Though the synthesis of phakellin was accomplished via a different type of cylization, i.e., oxidative cyclization instead of intramolecular C-H insertion (*vide supra*, Chapter V), this pathway is also applicable towards palau'amine synthesis.

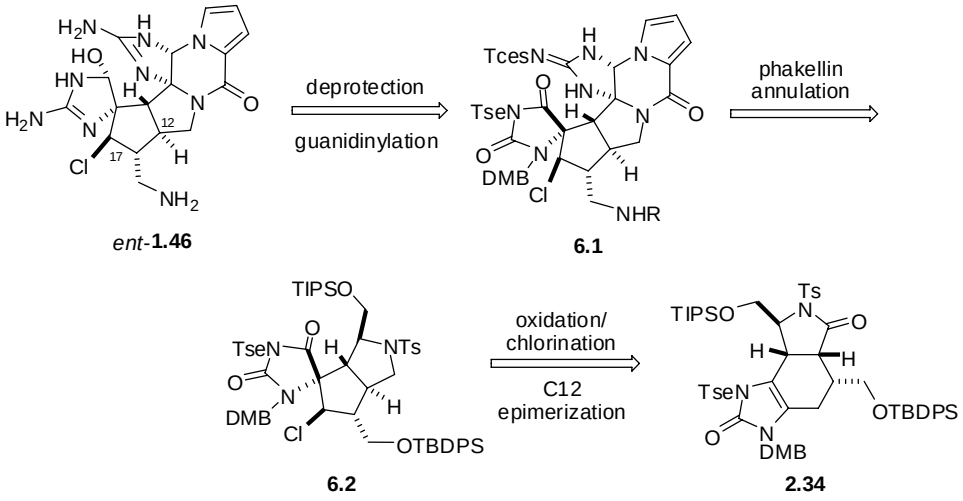
Scheme 61



The recent structural revision of palau'amine however, prompted us to reconsider our initial strategy towards palau'amine, as the stereochemistry of two carbon centers on the cyclopentane core was revised (Figure 8, Chapter I), opposite to what was accepted for 14 years since the 1993 isolation report.[34-37] Comparing the advanced intermediate **4.51**, which was originally intended for C17 epi-palau'amine synthesis, with the revised structure of palau'amine (*ent*-**1.46**, absolute stereochemistry still not determined), it is

easy to see that the chlorine-bearing C17 actually has the correct stereochemistry while the stereochemistry of C12 needs to be inverted (Scheme 62).

Scheme 62

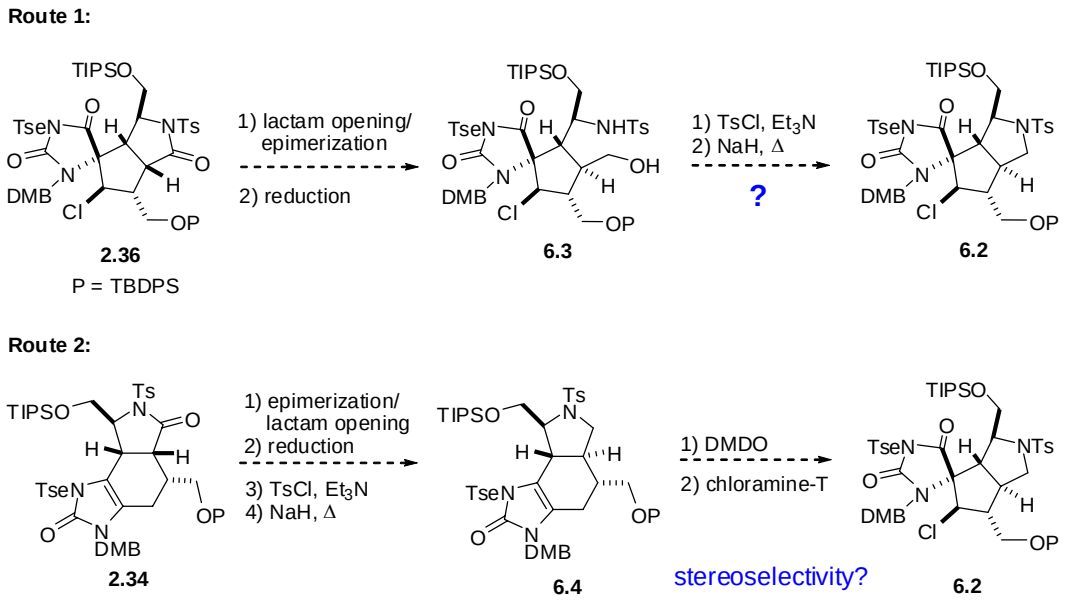


The revised palau'amine structure has a highly strained *trans*-fused azabicyclo-[3.3.0]octane moiety, which is rarely seen in literature.[37] Therefore the initial challenge of our new synthetic plan is to build a highly strained *trans*-fused five-five bicyclic system (**6.2**). Once this unusual structure is obtained, the following phakellin annulation could take advantage of the chemistry developed for phakellin synthesis, to give a hexacyclic advanced intermediate **6.1**, which possesses all the necessary components for palau'amine. Late stage guanidinylation and deprotection would then deliver palau'amine.

B. Strategies toward the Revised Structure

The rarely seen *trans*-fused azabicyclo[3.3.0]octane structure presents a significant challenge for our synthesis. Entry into this unusual ring system directly via a Diels-Alder cycloaddition was no longer a suitable option. Due to the very limited known methods to generate this type of structures,[86] either a complete overhaul of synthetic plan, or an elaboration of the current strategy was necessary. Now that the relative stereochemical arrangement of the substituents on the cyclopentane core of palau'amine is identical to that of axinellamine, another target of interest in our laboratories, we can apply part of the methods used for axinellamine synthesis, namely the C12 epimerization method,[87] to the new palau'amine target.

Scheme 63



Our initial thoughts on strategies to construct the *trans*-azabicyclo[3.3.0]octane system involved an intramolecular S_N2 cyclization to form spiro tricycle **6.2**, after epimerization of the C12 (Scheme 63, Route 1). However, whether this seemingly straightforward strategy will work is questionable, as there is no literature precedent of using similar type of reactions to build *trans*-fused five-five bicyclic structures. In addition, molecular models of the epimerized intermediate **6.3** also suggest that approach of the sulfonamide nitrogen to the carbon bearing a tosylate leaving group in an S_N2 fashion is unlikely to happen.

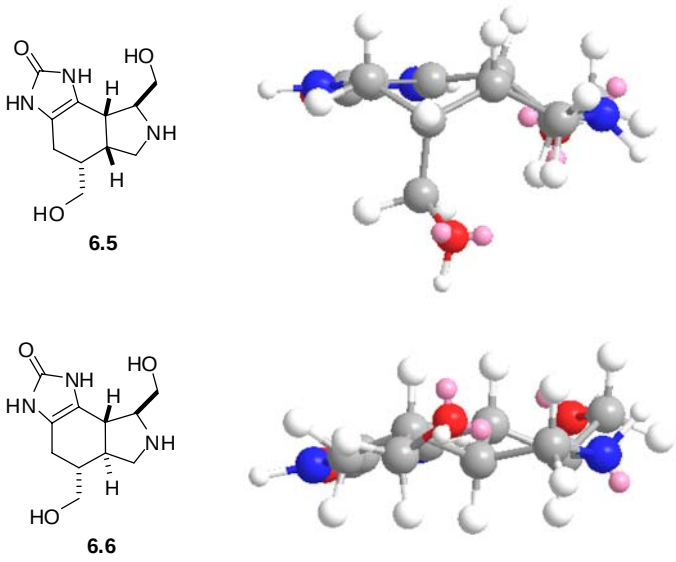


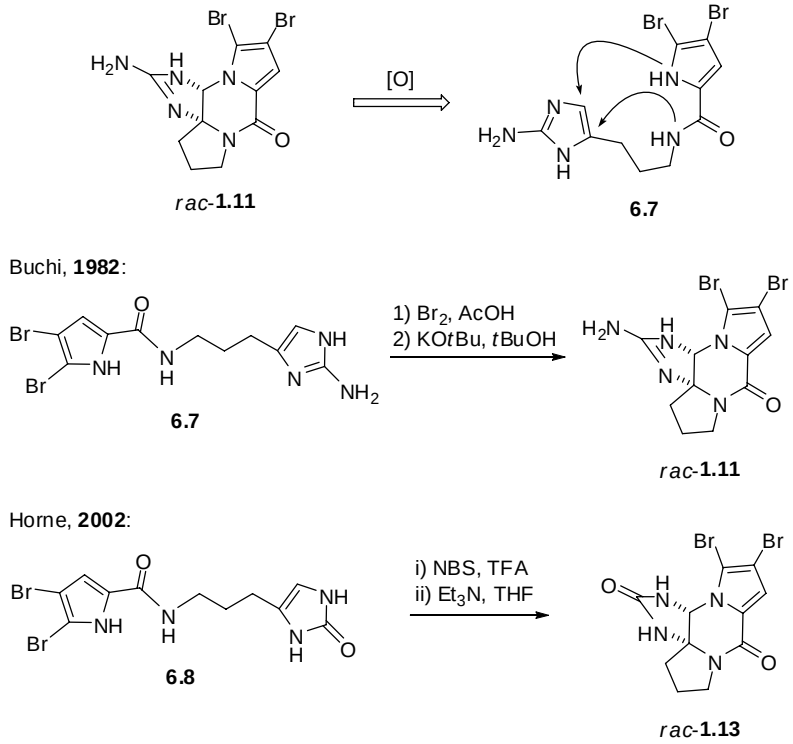
Figure 17. Comparison of the molecular models of *cis*-fused and *trans*-fused six-five systems (protecting groups removed for clarity)

Another approach is to form the *trans*-fused five-six bicyclic system **6.4** first, which should be much easier than building a *trans*-fused five-five bicyclic system, and

make the chlorinated spirocycle subsequently (Scheme 63, Route 2). The major concern of this route is the stereoselectivity of the oxidation/chlorination. Diels-Alder adduct **2.34** has a distinctive cup-shaped molecular conformation, as shown in the simplified model **6.5** (Figure 17). The shape of the molecule only allows the oxidant and chlorinating reagent to approach the corresponding reaction centers from the convex face, yielding spirocycle **2.36** as the only observed stereoisomer. Once the C12 is epimerized, the molecular shape will change drastically to a relatively flat conformation, as shown in the simplified model **6.6** (Figure 17). This change of molecular shape could result in low diastereoselectiviy for the oxidation/chlorination sequence.

Preliminary results from the studies on the second route were not encouraging, as we encountered difficulties on epimerization of C12 in Diels-Alder adduct **2.34**. Alternatively, our attention was directed to the original synthesis of racemic dibromophakellin (*rac*-**1.11**) by Büchi and co-workers.[67] The synthesis took advantage of an oxidative cyclization process to rapidly assemble the tetracyclic oroidin alkaloid *rac*-**1.11** from the acyclic dihydrooroidin **6.7** (Scheme 64). Two decades later, Horne and co-workers applied the same strategy on the synthesis of racemic dibromophakellstatin (*rac*-**1.13**) from an acyclic imidazolone precursor **6.8**.[68a] Since a phakellin moiety resides in the palau'amine skeleton, this method of making dibromophakellin hints a promising strategy applicable to palau'amine synthesis. A similar reaction pathway was actually proposed by Al-Mourabit and Potier as a possible biogenesis of palau'amine (Chapter I, Scheme 2).[8]

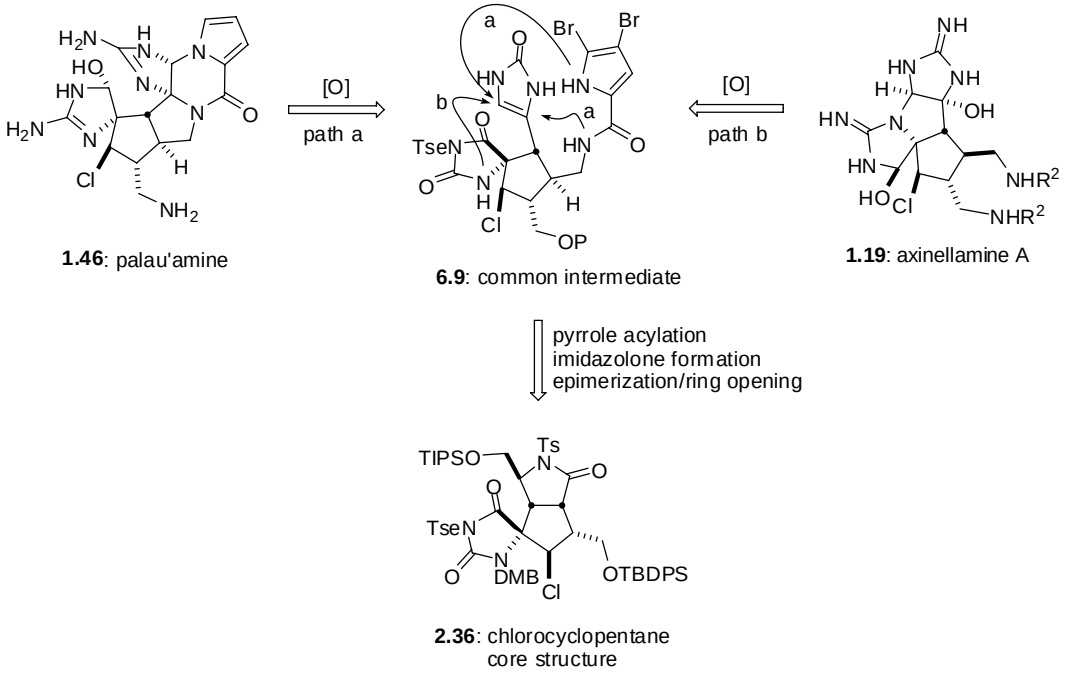
Scheme 64



Al-Mourabit's biosynthetic proposal for palau'amine prompted us to reconsider our initial common intermediate strategy towards palau'amine and axinellamine, and allowed us to design another common-intermediate-type synthetic plan (Scheme 65) in which the point of divergence would occur at a much later stage compared with the original strategy (Chapter III, Scheme 15). As the revised structure of palau'amine shares the same cyclopentane moiety with axinellamine, we envisioned a late stage intermediate **6.9** (Scheme 65) that would possess all the necessary carbon framework of both structures. C12 epimerization could be achieved from spirocycle **2.36** via a known method developed in our studies towards axinellamine synthesis.[87] Subsequent imidazolone formation and pyrrole-acylation would incorporate the two necessary

functionalities for oxidative cyclizations (path a). With the common intermediate **6.9** in hand, the two natural products would then be accessed through different modes of oxidative cyclization, building on proposals by Al-Mourabit and Potier.[8]

Scheme 65



1.46: palau'amine

6.9: common intermediate

1.19: axinellamine A

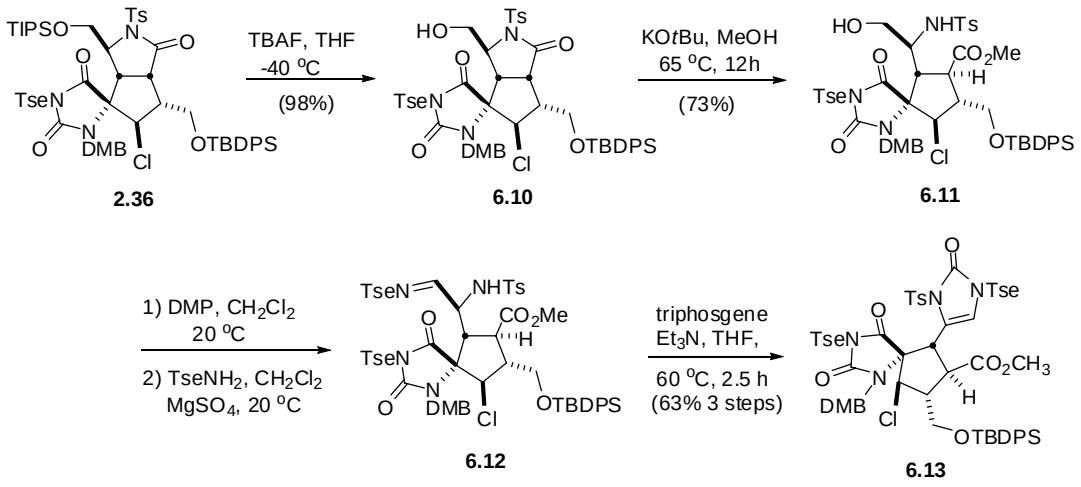
2.36: chlorocyclopentane core structure

C. Synthesis of a Common Intermediate

Starting from tricycle **2.36**, obtained from the oxidation/chlorination of Diels-Alder adduct **2.34** as described before, selective removal of the TIPS protecting group over TBDPS yielded alcohol **6.10**. After treatment of alcohol **6.10** with potassium *tert*-butoxide in methanol (Scheme 66) and heating the reaction to 65 °C for 12 h, C12-epimerized ester **6.11**, which features the fully functionalized cyclopentane core of both palau'amine and axinellamine, was pleasingly isolated in good yield.[87] With epimerized

ester **6.11** in hand we then applied a 3-step sequence to generate imidazolone **6.13** in good yield. Dess-Martin oxidation of the free alcohol moiety of **6.11** produced the corresponding aldehyde quantitatively. Treatment of the aldehyde intermediate with tosylethylamine ($TseNH_2$) smoothly formed an imine intermediate **6.12**, which was then directly treated with triphosgene in the presence of triethylamine in THF at 65°C, providing the desired imidazolone **6.13** in 45-65 % yield over the three steps after flash chromatography purification.

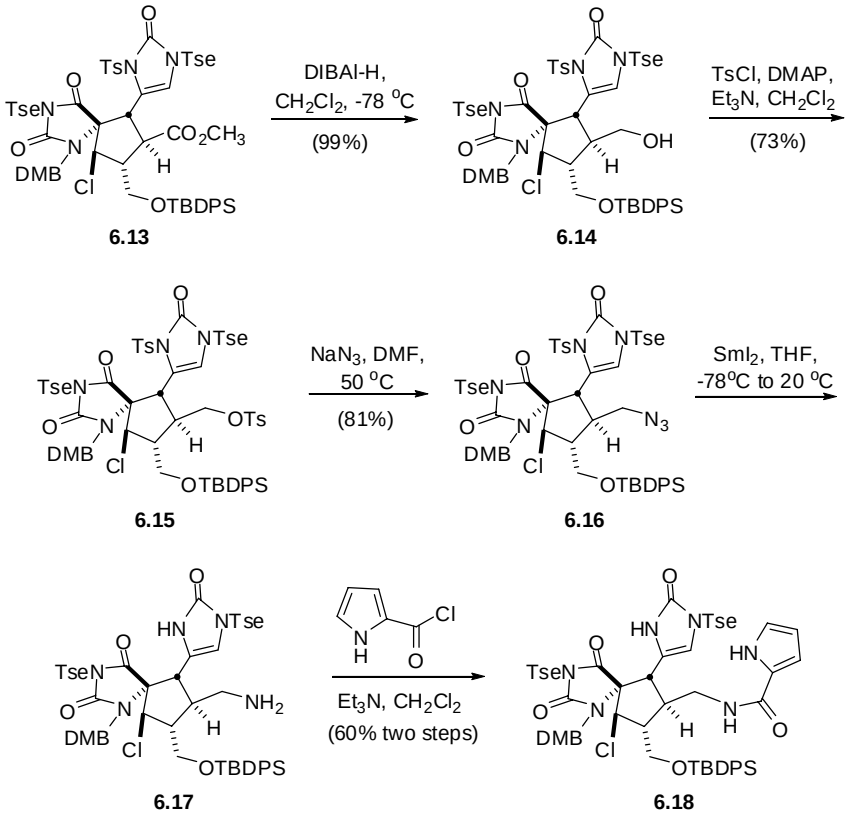
Scheme 66



Reduction of the methyl ester **6.13** with DIBAl-H proceeded smoothly at low temperature and delivered the corresponding primary alcohol **6.14** quantitatively and in sufficient purity to be used directly for the following step (Scheme 67). Conversion of the primary alcohol into its corresponding tosylate **6.15**, and subsequent S_N2 displacement of the tosylate functionality by azide anion afforded azide **6.16**. Use of

DPPA under Mitsunobu conditions on alcohol **6.14** only led to the isolation of a phosphate. Treatment of azide **6.16** with excess samarium diiodide accomplished both the reduction of azide[64] and the removal of imidazolone tosyl protecting group, leaving the tosylethyl groups unaffected. Primary amine **6.17** was then acylated with pyrrole-2-carbonyl chloride[61] generating the pyrrole-imidazolone intermediate **6.18**, which is a viable precursor to palau'amine via intramolecular oxidative bis-cyclization (*vide supra*).

Scheme 67



D. Conclusion

The synthesis of an advanced bio-inspired common intermediate **6.18** toward palau'amine, axinellamine and potentially styloguanidine and massadine was accomplished. Building on our previous work, spirocyclopentane **2.36** (obtained from Diels-Alder adduct **2.34** via oxidation/chlorination/ring contraction) was concisely converted to imidazolone **6.13** through a C12 epimerization and a three-step cyclization sequence. Elaboration of one of the chlorocyclopentane side-chains then efficiently delivered pyrrole **6.18**, a suitable precursor not only for the palau'amine synthesis, but also for axinellamine synthesis.

CHAPTER VII

CONCLUSION

In summary, our synthetic efforts towards palau'amine and related oroidin-alkaloids have been a rewarding adventure with many interesting chemistry being discovered and advanced synthetic intermediates being reached. After unsuccessful studies on obtaining the chlorine bearing C17 stereochemistry for the originally proposed palau'amine structure, we shifted our synthetic efforts toward the epi-chloro palau'amine (C17-epimer **4.3**, Figure 18). An advanced pentacyclic intermediate **4.51** bearing the whole carbon framework of palau'amine was synthesized from the Diels-Alder adduct **2.34** via a 14-step sequence. After reaching this stage, thorough examination of the coupling constants and NOESY data revealed some significant discrepancies with the original palau'amine isolation data. In light of recent structural revision of palau'amine, it was found that pentacycle **4.51** actually has correct stereochemistry at C17 but wrong stereochemistry at C12.

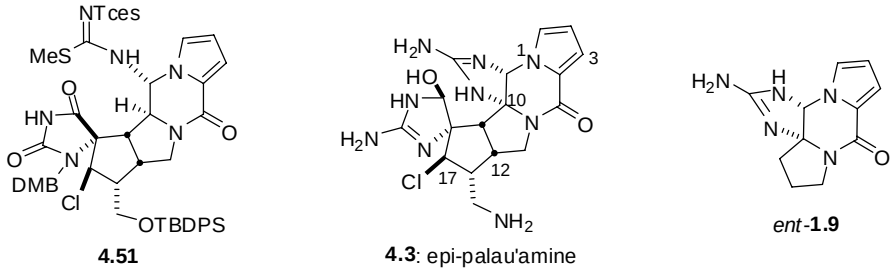
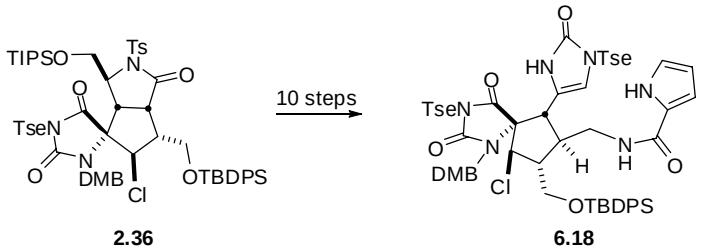


Figure 18. Structures of pentacycle **4.51** and initial target epi-palau'amine **4.3**

In a model study of the phakellin annulation strategy for palau'amine synthesis, the first enantioselective total synthesis of two members of the phakellin family of pyrroloimidazole alkaloids, i.e., (+)-phakellin (*ent*-**1.9**) and (+)-monobromophakellin (*ent*-**1.10**), was accomplished. The synthesis relies on a unique oxidative cyclization from a chiral tricyclic guanidine precursor (**5.17**) and results in a highly concise, enantioselective route to these targets. Importantly, these results were valuable contributions to palau'amine synthesis as it provides an expedient annulation strategy onto cyclopentane precursors.

Scheme 68



2.36 **6.18**

With the revised palau'amine structure, we envisioned a common intermediate synthetic plan towards palau'amine, axinellamine and related congeners. The synthesis of an advanced bio-inspired common intermediate **6.18** was accomplished through a 10-step sequence starting from spirocyclopentane **2.36** (Scheme 68).

CHAPTER VIII

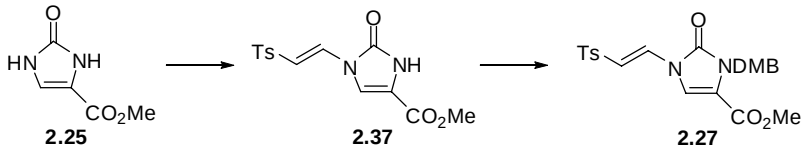
EXPERIMENTAL PROCEDURES

General Information

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried (120 °C) glassware unless noted otherwise. Tetrahydrofuran (THF, EM Science) and diethyl ether (Et_2O, EM Science) were distilled prior to use from sodium metal. Methylene chloride (or dichloromethane, CH_2Cl_2, EM Science) and benzene (PhH, EM Science) were distilled from calcium hydride prior to use. Methanol (MeOH, EM Science) was distilled from magnesium methoxide. *N*,*N*-Dimethylformamide (DMF, ACROS) and methyl sulfoxide (DMSO, ACROS) were used as purchased (extra dry, with molecular sieves, water<50 ppm). Alternatively, solvents (THF, CH_2Cl_2, CH_3CN, toluene) used for reations were obtained from a solvent purification system using activated molecular sieves drying column (MBRAUN solvent purification system). Triethylamine (Et_3N), 2,6-lutidine, pyridine and diisopropylethylamine (DIEA, Hünig's base) were distilled from calcium hydride or potassium hydroxide prior to use. Brine refers to a saturated water solution of sodium chloride. Rochelle's salt solution refers to 2 M aqueous solution of sodium potassium tartrate. Solutions of dimethyldioxirane (DMDO)[42] in acetone, 2-iodoxybenzoic acid (IBX)[88] and pyrrole-2-carbonyl chloride[61] were prepared according to literature procedures. All other commercially available reagents were used as received unless specified otherwise.

^{1}H-NMR chemical shifts are reported as δ values in ppm relative to solvent standard chemical shifts ($CDCl_3$: 7.26 ppm, benzene-d_6: 7.16 ppm, DMSO-d_6: 2.50, CD_3CN: 1.94, CD_3OD: 3.31 ppm).[89] ^{1}H-NMR coupling constants (*J*) are reported in Hertz (Hz), and multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet), dd (doublet of doublets), dt (doublet of triplets), and so on. ^{13}C-NMR chemical shifts are reported as δ values in ppm relative to solvent standard chemical shifts.[89] ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Varian Inova-300, Mercury-300, or Varian Inova-500 spectrometer. Infrared spectra were recorded with a Nicolet Impact 410 FTIR spectrometer, or with a Bruker Tensor® 27 FTIR sepectrometer. Mass spectra were obtained on a VG analytical 70S high resolution, double focusing, sectored (EB) mass spectrometer (for FAB), a MDS Sciex (Concord, Ontario, Canada) API Qstar Pulsar (for ESI), or a ThermoFinnigan (San Jose, California) LCQ Deca Mass Spectrometer (for APCI) at the Mass Spectrometry Application and Collaboration Facility (Texas A&M University). Flash column chromatography was performed using 60Å Silica Gel (EM Science, 230-400 mesh) as a stationary phase. Thin layer chromatography (TLC) was performed using silica gel $60F_{254}$ glass TLC plates (EMD Chemicals Inc., 250 μm layer thickness). Enantiomeric excess (*ee*) was determined by HPLC analysis (RAININ SD-200 with DYANMAX UV-C DETECTOR) using a Chiralpak® AD column. Microwave reactions were carried out in a CEM® Explorer™/Discover™ microwave system. Reverse phase preparative HPLC was carried out on a BECKMAN COULTER® HPLC system.

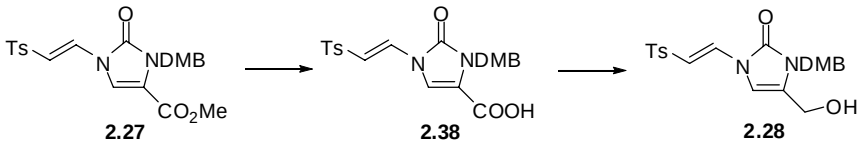
Experimental Procedures



Imidazolone ester 2.27: To a stirred solution of ester **2.25**[90] (3.80 g, 26.7 mmol) in 200 mL of DMF at 25 °C was added 80% sodium hydride (722 mg, 24.1 mmol), the resulting mixture was stirred for 15 mins. To the slurry was added dropwise a solution of 1,2-di-*p*-toluenesulfonylethylene[46] (6.30 g, 18.7 mmol) in 100 mL of DMF. Stirring was continued for 13 h, the reaction was cooled to 0 °C and then ethyl acetate (200 mL) and water (200 mL) were added to quench the reaction. The organic layer was washed with water (6 X 100 mL) and dried ($MgSO_4$). Solvents were removed *in vacuo* and the crude solid was purified by dissolving the impurties in ethyl acetate and filtering the residue to afford the Tsv protected imidazolone ester **2.37** (3.41 g, 56%) as a tan-greenish powder. **2.37**: R_f = 0.45 (8% MeOH/CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ = ~8.0 (bs, 1H), 7.76-7.81 (m, 3H), 7.34 (d, 2H), 7.06 (s, 1H), 6.79 (d, 1H), 3.88 (s, 3H), 2.45 (s, 3H); IR (thin film) 1637, 1700, 2850 cm^{-1}.

To a solution of ester **2.37** (13.35 g, 41.4 mmol) in 300 mL of DMF at 25 °C was added potassium carbonate (6.30 g, 45.6 mmol), followed by DMBCl[91] (8.10 g. 43.5 mmol). The reaction was warmed to 60 °C and stirring continued for 16 h, on cooling to 25 °C the reaction was diluted with 200 mL of ethyl acetate and washed with water (6 X 100 mL). The organic layer was dried ($MgSO_4$). Solvents were removed *in vacuo* to

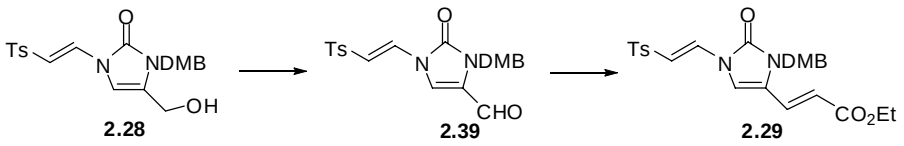
afford the ester **2.27** (19.56 g, 99%) which was of sufficient purity to be taken onto the next step without purification. A small sample of crude **2.27** was taken and purified by flash chromatography for analysis (silica gel, EtOAc/hexanes, 2/5) affording ester **2.27** as a colorless foam: R_f = 0.31 (EtOAc/hexanes, 2/5); IR (Neat) 3073, 2843, 1716, 1632, cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 14.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.12 (s, 1H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.85 (d, *J* = 14.0 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 5.13 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 2.43 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 159.1, 151.3, 148.8, 148.6, 144.5, 137.8, 132.9, 130.0, 129.3, 127.5, 120.8, 117.0, 116.6, 115.8, 111.7, 110.9, 55.9, 55.8, 52.1, 45.4, 21.6; HRMS (ESI) calcd for $C_{23}H_{25}N_2O_7S$ [M+H]: 473.1382; found: 473.1410.



Allylic alcohol 2.28: To a stirred solution of crude ester **2.27** (19.56 g, 41.4 mmol) in 400 mL of THF/H_2O (v/v; 3/1) at 25 °C was added LiOH (1.14 mg, 47.5 mmol) stirring continued for 2 h and then THF was removed *in vacuo*. EtOAc (400 mL) was added and the mixture extracted (the organic phase was discarded). 1M HCl (500 mL) was added to the aqueous phase and extracted with EtOAc (3 X 500 mL). Organic layers were combined and dried ($MgSO_4$). Solvents were removed *in vacuo* and the crude acid **2.38** isolated as a yellow foam (18.20 g, 96%): R_f = 0.15 (EtOAc); ^{1}H-NMR (300 MHz,

$CDCl_3$) δ= 7.77-7.85 (m, 3H), 7.32 (d, 2H), 7.24(s, 1H), 6.87-6.98 (m, 3H), 6.75 (d, 1H), 5.14 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.44 (s, 3H); IR (thin film) 1631, 1712 cm^{-1}.

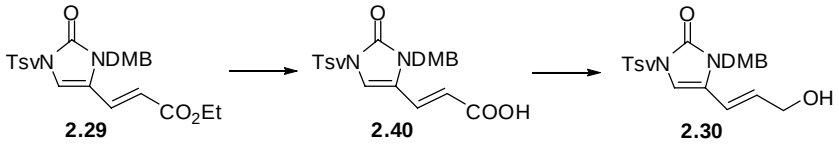
The crude acid **2.38** (18.10 g, 39.5 mmol) was dissolved in 400 mL of THF and 0.5 mL of DMF at 25 °C, oxalyl chloride (3.70 mL, 43.4 mmol) was added dropwise to the solution and the mixture was stirred for 1h. The reaction mixture was cooled to -78 °C and $LiBH_4$ in THF (2M, 59.2 mL, 118.4 mmol) was added dropwise. The reaction mixture was stirred for 2 h, 100 mL of H_2O was added to quench the reaction and then THF was removed *in vacuo*. EtOAc (500 mL) was added and the mixture extracted. 1M HCl (500 mL) was added to the aqueous phase and extracted with EtOAc (3 X 500 mL). Organic layers were combined and dried ($MgSO_4$). Solvents were removed *in vacuo* and the crude alcohol **2.28** (17.08 g, 97%) isolated as a yellow solid which was of sufficient purity to be taken onto the next step without purification. A small amount was purified by flash chromatography for analysis (SiO_2, EtOAc/hexanes, 2/5) to afford alcohol **2.28** as a yellow solid. R_f = 0.14 (EtOAc/hexanes, 4/1); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 14.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 2.0, 1H), 6.81 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 14.0 Hz, 1H), 6.31 (s, 1H), 4.87 (s, 2H), 4.29 (s, 2H), 3.827 (s, 3H), 3.825 (s, 3H), 2.50 (br s, 1H), 2.42 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 152.2, 149.5, 149.0, 144.6, 138.5, 133.9, 130.2, 129.0, 127.5, 127.4, 120.1, 113.2, 111.4, 111.1, 105.4, 56.2, 56.1, 55.3, 45.2, 21.8; IR (film) 3466, 1711 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{25}N_2O_6S$ [M+H]: 445.1407. Found: 445.1407.



Ethyl ester 2.29: To a solution of activated manganese dioxide (heated with heat gun under vacuum) (32.4 g, 373 mmol) in 60 mL of dichloromethane at 25 °C was added a solution of allylic alcohol **2.28** (13.8 g, 31.0 mmol) in 400 mL of dichloromethane. The resulting solution was stirred for 12 h and filtered through a pad of Celite®. Solvents were removed *in vacuo* and the crude aldehyde **2.39** (9.90 g, 72%) was isolated as a yellow solid: R_f = 0.63 (EtOAc); IR (thin film) 2937, 2837, 1672, 1731 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ= 9.38 (s, 1H), 7.78-7.83 (m, 3H), 7.33 (d, 2H), 7.15 (s, 1H), 6.97-7.05 (m, 3H), 6.76 (d, 1H), 5.13 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.44 (s, 3H).

A solution of triethylphosphonoacetate (4.78 mL, 24.1 mmol) in 100 mL of THF was cooled to 0 °C and treated with 80% NaH (658 mg, 21.9 mmol), allowed to warm to 25 °C and stirred for an additional 40 min. The resulting solution was added dropwise to a solution of crude aldehyde **2.39** (9.70 g, 21.9 mmol) in 300 mL of THF and stirring was continued for 30 min. The reaction was quenched with 50 mL of pH 4 buffer solution. THF was removed *in vacuo* and the aqueous phase was extracted with EtOAc (3 X 300 mL). The organic layers were combined and dried ($MgSO_4$). Solvents were removed *in vacuo* and the crude ester **2.29** isolated as a yellow oil (13.2 g). A small amount was taken and purified by flash chromatography for analysis (silica gel, 40% EtOAc/hexanes) to afford ester **2.29** as a colorless foam. R_f = 0.41 (EtOAc/hexanes, 2/3); IR (film) 3120, 2937, 2838, 1712 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 14.0

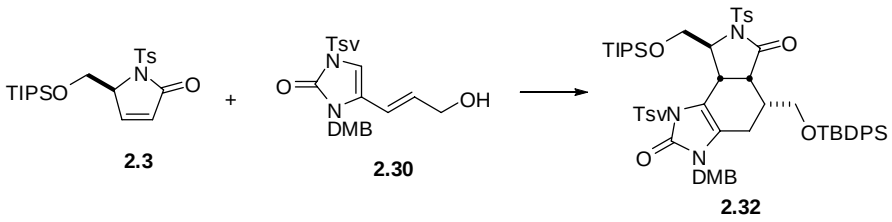
Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 16.0 Hz, 1H), 6.80-6.76 (m, 4H), 6.67 (d, *J* = 14.0 Hz, 1H), 6.14 (d, *J* = 16.0 Hz, 1H), 4.89 (s, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.43 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.1, 151.8, 149.6, 149.1, 144.7, 138.7, 133.2, 130.2, 128.8, 128.3, 127.7, 124.3, 119.7, 119.7, 115.3, 111.5, 110.6, 108.5, 61.2, 56.2, 56.1, 45.5, 21.9, 14.4; HRMS (ESI) calcd for $C_{26}H_{29}N_2O_7S$ [M+H]: 513.1695. Found: 513.1692.



Diene 2.30: To a stirred solution of crude ester **2.29** (13.2 g, 25.8 mmol) in 400 mL of THF/H_2O (v/v; 3/1) at 25 °C was added LiOH (788 mg, 32.9 mmol) and stirring was continued for 12h and then THF was removed *in vacuo*. EtOAc (150 mL) was added and the mixture extracted, the organic phase was discarded. 1M HCl (150 mL) was added to the aqueous phase and extracted with EtOAc (3 x 300 mL). Organic layers were combined and dried ($MgSO_4$). Solvents were removed *in vacuo* and the crude acid **2.40** was isolated as a yellow solid (8.10 g, 76%).

Due to the instability of the diene, a portion of the acid **2.40** (1.0 g, 2.06 mmol) was dissolved in 100 mL of THF at 0 °C, to the solution was added triethylamine (288 μL, 2.06 mmol), followed by methyl chloroformate (174 μL, 2.06 mmol) and the mixture was stirred for 15 min, or until TLC indicated complete formation of the mixed

anhydride. The reaction mixture was cooled to -78 °C and $LiBH_4$ in THF (2M, 2.06 mL, 4.13 mmol) was added dropwise. The reaction mixture was stirred for 15 min, 50 mL of H_2O was added to quench the reaction and solvents were removed *in vacuo*. Dichloromethane (100 mL) was added and the mixture extracted. 1M HCl (100 mL) was added to the aqueous phase and extracted with CH_2Cl_2 (3 X 200 mL). The organic layers were combined and dried ($MgSO_4$) and solvents were removed *in vacuo* and the crude alcohol **2.30** (972.0 mg, 99%) isolated as a yellow foam. R_f = 0.16 (EtOAc); ^{1}H-NMR (500 MHz, benzene-d_6) δ = 8.11 (d, *J* = 14.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.77-6.73 (m, 4H), 6.48 (d, *J* = 8.0 Hz, 1H), 6.02 (dd, *J* = 16.0, 1.0 Hz, 1H), 5.74 (dt, *J* = 16.0, 2.0 Hz, 1H), 5.45 (s, 1H), 4.55 (s, 2H), 3.77 (dd, *J* = 4.5, 2.0 Hz, 2H), 3.40 (s, 3H), 3.30 (s, 3H), 1.86 (s, 3H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 151.7, 150.3, 149.8, 143.3, 140.1, 133.6, 132.7, 129.8, 129.75, 129.7, 125.9, 119.8, 114.9, 113.9, 112.1, 111.8, 102.9, 62.3, 55.5, 55.4, 44.7, 21.0; IR (film) 3391, 3063, 2935, 1721 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{27}N_2O_6S$ [M+H]: 471.1590. Found: 471.1609.

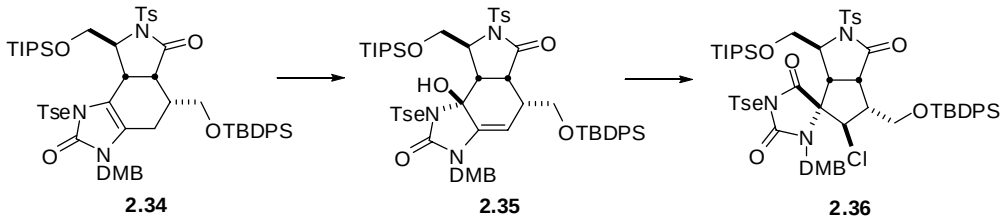


Tsv/DMB Diels-Alder adduct 2.32: To a solution of crude diene **2.30** (10.0 mg, 0.020 mmol) in 1.0 mL of benzene at 25 °C in a sealed tube was added dienophile **2.3** (9.0 mg,

0.020 mmol), followed by 2,6-lutidine (1.85 μL, 0.016 mmol). The resulting solution was stirred for 24 h at 95 °C. Further portions (10.0 mg, 0.02 mmol) of crude **2.30** were added every 24 h until 4 equivalents had been added. Solvents were removed *in vacuo* and the crude oil was purified by passing through a plug of silica gel (washing with EtOAc) to afford recovered dienophile **2.3** (5.0 mg) and a single Diels-Alder regioisomer as a colorless oil (~80% purity).

A solution of the Diels-Alder adduct in 3 mL of dichloromethane at 25 °C was treated with TBDPSCl (3.20 μL, 0.011 mmol), followed by triethylamine (1.7 μL, 0.012 mmol) and DMAP (catalytic). After 24 h at 25 °C, solvents were removed *in vacuo* and the crude oil was purified by flash chromatography (SiO_2, 30% EtOAc/hexanes) to afford silyl ether **2.32** (11.5 mg, 48%) as a clear oil: R_f = 0.73 (EtOAc/hexanes, 2/3); ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.93 (d, *J* = 8.5 Hz, 2H), 7.79 (s, 2H), 7.76-7.73 (m, 4H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.27-7.24 (m, 6H), 6.88 (d, *J* = 2.0 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.71 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.61 (d, *J* = 8.5 Hz, 2H), 6.55 (d, *J* =8.0 Hz, 1H), 4.68 (d, *J* = 15.0 Hz, 1H), 4.27 (dd, *J* = 10.5, 3.5 Hz, 1H), 4.23 (dd, *J* = 7.0, 3.5 Hz, 1H), 4.19 (d, *J* = 8.0 Hz, 2H), 3.97 (dd, *J* =10.5, 7.0 Hz, 1H), 3.68 (d, *J* = 15.0 Hz, 1H), 3.43 (s, 3H), 3.36 (s, 3H), 3.29 (dd, *J* = 6.0, 3.0 Hz, 1H), 3.20 (m, 1H), 2.13 (ddd, *J* = 16.0, 5.0, 1.5 Hz, 1H), 1.95 (s, 3H), 1.88 (ddd, *J* = 16.0, 11.0, 3.0 Hz, 1H), 1.84 (s, 3H), 1.71 (m, 1H), 1.17-1.13 (m, 30H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 172.4, 151.9, 150.5, 150.1, 145.0, 143.6, 140.0, 135.8, 135.4, 133.7, 133.6, 132.4, 130.1, 130.0, 129.5, 129.2, 128.1, 127.5, 127.4, 123.9, 120.3, 116.6, 112.14, 112.09, 112.07, 64.8, 64.5, 62.4, 55.6, 55.5, 44.5, 41.4, 36.7, 34.3, 27.0, 21.3, 21.0, 19.8, 19.3, 18.3, 18.2, 12.0; IR (film)

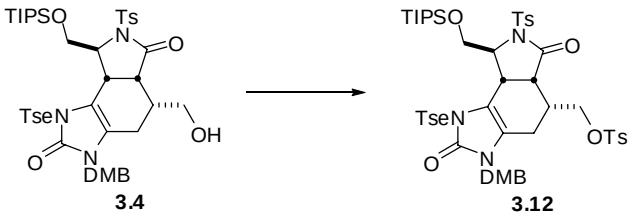
2941, 2864, 1723 cm^{-1}; HRMS (ESI) calcd for $C_{61}H_{78}N_3O_{10}S_2Si_2$ [M+H]: 1132.4667. Found: 1132.4666.



Spirocycle 2.36: A solution of TBDPS-protected Diels-Alder adduct **2.34** (500 mg, 0.440 mmol) and magnesium sulfate (100 mg) in 40 mL of dichloromethane was cooled to –50 °C and treated with dimethyldioxirane (0.06M in acetone, 8.1 mL, 0.48 mmol) after 3 h the reaction was quenched with 100 μL of methyl sulfide. Solvents were removed *in vacuo* to afford crude allylic alcohol **2.35** (500 mg, 99%) as a colorless foam.

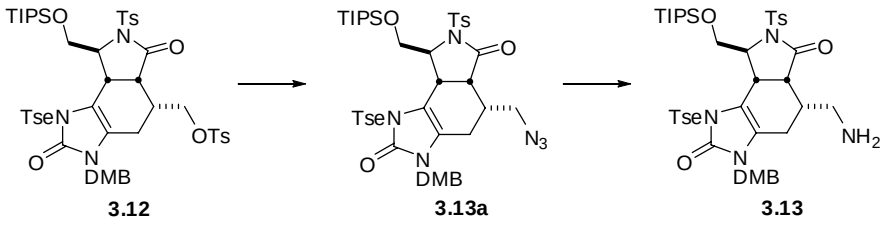
The crude allylic alcohol **2.35** was redissolved in 40 mL of dichloromethane and cooled to –50 °C. Cyclohexene (223 μL, 2.20 mmol) was added, followed by magnesium sulfate (100 mg) and chloramine-T (200 mg, 0.88 mmol). The reaction mixture was allowed to warm to 25 °C, and then stirred for a total of 12 h. The reaction was quenched with 20 mL of water and the aqueous layer was extracted with CH_2Cl_2 (3 X 50 mL). The organic layers were combined, dried ($MgSO_4$), concentrated *in vacuo*, and the crude oil was purified by flash chromatography (SiO_2, EtOAc/hexanes, 1:3) to afford cyclopentane **2.36** as a colorless foam (339 mg, 65%). R_f = 0.72 (60% EtOAc/hexanes); $[\alpha]_D$ -33.6 (*c* 1.17, CH_2Cl_2); IR (film) 3067, 2859, 1776, 1723 cm^{-1};

^{1}H-NMR (500 MHz, benzene-d_6) δ 8.26 (d, J = 8.5 Hz, 2H), 7.96-7.94 (d, J = 8.0, 2.0 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H), 7.81-7.79 (m, 2H), 7.46 (d, J = 2.0 Hz, 1H), 7.39 (dd, J = 8.0, 2.0 Hz, 1H), 7.28-7.20 (m, 6H), 6.84 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 6.39 (d, J = 8.0 Hz, 1H), 5.87 (d, J = 16.0 Hz, 1H), 4.90 (s, 1H), 4.74 (d, J = 16.0 Hz, 1H), 4.55 (t, J = 10.0 Hz, 1H), 4.50 (d, J = 12.5 Hz, 1H), 4.23 (dd, J = 10.0, 2.0 Hz, 1H), 4.11 (m, 2H), 3.96 (t, J = 8.0 Hz, 1H), 3.80 (d, J = 8.0 Hz, 1H), 3.79-3.73 (m, 1H), 3.62 (s, 3H), 3.58-3.53 (ddd, J = 15.0, 9.0, 3.0 Hz, 1H), 3.39-3.34 (ddd, J = 15.5, 7.0, 3.0 Hz, 1H), 3.27 (s, 3H) 3.26-3.21 (ddd, J = 15.0, 9.0, 3.0 Hz, 1H), 2.95-2.90 (ddd, J = 15.5, 7.0, 3.0 Hz, 1H), 1.87 (s, 3H), 1.84 (s, 3H), 1.20 (s, 9H), 0.98-0.90 (m, 21H); ^{13}C NMR (125 MHz, benzene-d_6) δ 173.23, 171.70, 156.73, 150.18, 149.81, 144.91, 144.73, 136.37, 136.16, 135.95, 135.73, 133.82, 133.60, 129.83, 129.80, 129.76, 129.73, 129.57, 129.41, 129.05, 129.03, 127.96, 126.62, 121.42, 112.93, 112.05, 76.67, 65.35, 61.09, 60.47, 59.86, 55.67, 55.23, 50.49, 49.03, 48.47, 47.15, 45.92, 33.29, 26.98, 21.08, 21.03, 19.41, 18.09, 18.03, 12.09; HRMS (ESI) calcd for $C_{61}H_{78}ClN_3O_{11}S_2Si_2$ [M+Li]: 1190.4465, found: 1190.4477.



Tosylate 3.12: To a mixture of alcohol **3.4** (35 mg, 0.039 mmol) and TsCl (11 mg, 0.059 mmol) was added anhydrous CH_2Cl_2, followed by triethylamine (~80 μL, excess). Let

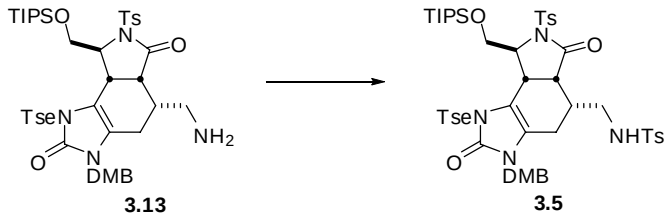
stand at 20 °C and stirred vigorously. After 36 h, the reaction mixture was extracted with CH_2Cl_2 (3 X 10 mL) and H_2O (10 mL). The organic layer was washed with sat'd $NaHCO_3$ and brine, and then dried over Na_2SO_4. Purification by column chromatography (silica gel, 50 → 80% EtOAc/Hexane) afforded tosylate **3.12** as a colorless foam (35 mg, 85%). R_f = 0.61 (EtOAc); $[\alpha]_D$ -48.0 (*c* 1.00, CH_2Cl_2); IR (thin film) 2940, 2863, 1742, 1690 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.75 (d, *J* = 8.0 Hz, 4H), 7.60 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.81 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 8.0 Hz, 1H), 4.58 (d, *J* = 15.5 Hz, 1H), 4.47 (dd, *J* = 8.0, 10.0 Hz, 1H), 4.38 (dd, *J* = 7.0, 10.0 Hz, 1H), 4.32 (m, 2H), 4.04-4.17 (m, 4H), 3.88 (m, 1H), 3.74 (d, *J* = 6.5 Hz, 1H), 3.60 (s, 3H), 3.37 (s, 3H), 3.22 (dd, *J* = 3.0, 7.0 Hz, 1H), 2.86 (dt, *J* = 4.0, 14.0 Hz, 1H), 2.06 (dd, *J* = 4.0, 15.0 Hz, 1H), 1.92 (s, 3H), 1.86 (s, 3H), 1.85 (s, 3H), 1.76 (m, 1H), 1.17-1.20 (m, 21H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 172.83, 153.76, 150.50, 149.74, 144.78, 144.38, 144.20, 137.76, 135.92, 133.94, 130.19, 129.86, 129.71, 129.43, 128.21, 128.03, 127.82, 127.54, 119.89, 119.05, 114.32, 112.32, 111.88, 70.85, 66.60, 65.39, 64.59, 63.95, 59.93, 55.75, 55.49, 52.77, 44.34, 41.77, 36.32, 34.82, 34.31, 30.86, 30.09, 21.16, 21.05, 21.01, 19.73, 18.20, 18.19, 12.15; HRMS (ESI) calculated for $C_{52}H_{67}N_3O_{12}S_3Si$ [M+Li]: 1056.3816. Found: 1056.3789.



Amine 3.13: To the tosylate **3.12** (18.5 mg, 0.0176 mmol) in a dry flask was added NaN_3 (12 mg, 0.176 mmol) and anhydrous DMF (0.6 mL). The reaction vessel was purged with nitrogen and sealed with a polyethylene stopper (yellow cap). The reaction mixtures was heated to 100 °C and stirred for 16 h. Added water to the reaction mixture and extracted with CH_2Cl_2/H_2O. The organic layer was washed with brine and dried over Na_2SO_4. Azide **3.13a** was obtained in sufficient purity (16 mg, 99%) for next step reaction after removal of solvent *in vacuo*.

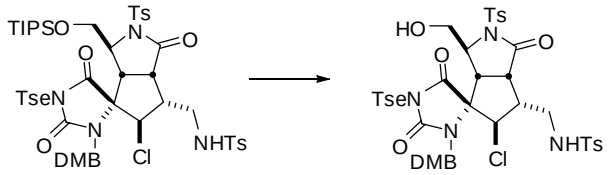
To a mixture of azide **3.13a** (38 mg, 0.041 mmol) and triphenylphosphine (54 mg, 0.20 mmol) in a dry flask was added THF (0.8mL), followed by water (25 μL). The reaction mixture was stirred vigorously at 20 °C. After 12 h, the reaction was stopped. Solvent was removed *in vacuo* and azotroped with benzene. The crude mixture was subjected to silica gel column purification (2 → 5% MeOH/CH_2Cl_2) to yield amine **3.13** (27.3 mg, 75%). R_f = 0.19 (7% MeOH/ CH_2Cl_2); ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.84 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.84 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.83 (d, *J* = 15.5 Hz, 1H), 4.37-4.43 (m, 2H), 4.13-4.22 (m, 3H), 4.05 (d, *J* = 15.5 Hz, 1H), 3.94 (m, 1H), 3.88 (d, *J* = 6.0 Hz, 1H), 3.58 (s, 3H), 3.50 (dd, *J* = 6.5, 3.0 Hz, 1H), 3.36 (s, 3H), 3.00 (dd, *J* = 12.5, 8.0 Hz, 1H), 2.83 (m, 1H), 2.71 (m, 1H), 2.06 (dd,

1H), 1.94 (s, 3H), 1.79-1.85 (m, 4H), 1.19-1.22 (m, 21H); MS (M+H): 895 (molecular unit mass $C_{45}H_{62}N_4O_9S_2Si$: 894).



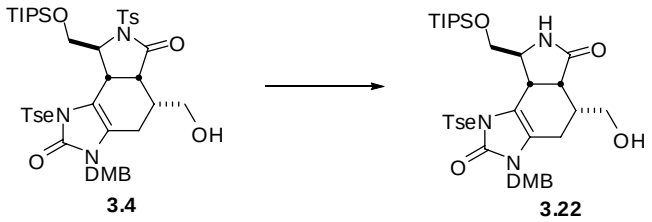
Sulfonamide 3.5: To a mixture of amine **3.13** (27 mg, 0.030 mmol) and *p*-toluenesulfonyl chloride (21 mg, excess) was added CH_2Cl_2 solvent (0.6 mL), followed by the addition of triethylamine (0.10 mL, excess). The reaction mixture was stirred at 20 °C for 20 h (the reaction mixture turned from light yellow color to brown). After the reaction time, the mixture was partitioned between CH_2Cl_2 and H_2O. The organic layer was washed with sat'd $NaHCO_3$ and brine and dried over Na_2SO_4. Silica gel column (50 → 75% EtOAc/Hexane) purification afforded sulfonamide **3.5** as a white solid (26 mg, 83%). R_f = 0.48 (80% EtOAc/Hexane); $[\alpha]_D$ -31.5 (*c* 0.80, CH_2Cl_2); IR (thin film) 2945, 2868, 2361, 1690 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.79 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.87 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.73-6.76 (m, 4H), 6.64 (d, *J* = 8.0 Hz, 1H), 4.94 (t, *J* = 6.5 Hz, 1H), 4.69 (d, *J* = 15.5 Hz, 1H), 4.35-4.38 (m, 2H), 4.10-4.24 (m, 4H), 3.91 (dt, *J* = 14.0, 6.0 Hz, 1H), 3.84 (d, *J* = 7.0 Hz, 1H), 3.65 (s, 3H), 3.39 (s, 3H), 3.28 (dd, *J* = 7.0, 3.0 Hz, 1H), 3.17-3.26 (m, 2H), 2.86 (dt, *J* = 14.0, 4.0 Hz, 1H), 2.11 (dd, *J* = 15.0, 3.5 Hz, 2H), 1.97 (s, 3H), 1.94 (s, 3H), 1.88 (s, 3H), 1.72 (m, 1H), 1.19-1.21 (m,

21H); ^{13}C NMR (125 MHz, benzene-d_6) δ 173.64, 153.81, 150.44, 149.67, 144.94, 144.25, 142.79, 138.17, 137.79, 135.83, 130.30, 129.75, 129.67, 129.53, 128.20, 127.59, 127.33, 119.94, 114.48, 112.31, 111.93, 65.29, 64.63, 55.83, 55.50, 52.74, 45.15, 44.35, 42.83, 36.32, 35.14, 34.78, 30.08, 21.20, 21.02, 20.50, 18.23, 18.22, 18.10, 12.17, 12.08; HRMS (ESI) calculated for $C_{52}H_{68}N_4O_{11}S_3Si$ [M+Li]: 1055.3976. Found: 1055.3530.



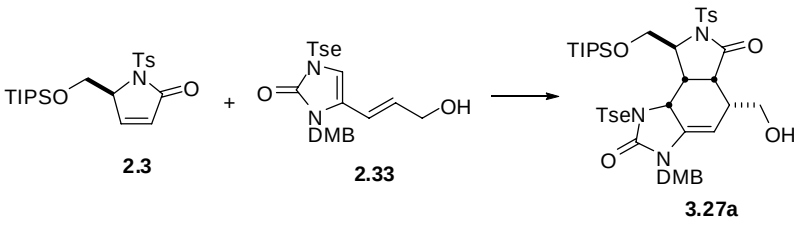
Alcohol 3.18: To a solution of chlorocyclopentane **3.17** (4.0 mg, 0.0036 mmol) in anhydrous THF (0.15 mL) was added TBAF (1.0 M solution in THF, 8 μL, 0.008 mmol) at -12 °C. The reaction was stirred at -12 °C for 1h. Water (5 mL) was added to the reaction and the resulting mixture was partitioned between water and CH_2Cl_2 (3 X 10 mL). The combined organics was washed with brine and dried over Na_2SO_4. After removal of solvent *in vacuo*, the crude product was purified by silica gel column (50 → 60% EtOAc/Hexanes) to yield the deprotected alcohol **3.18** (4 mg, 99%): R_f = 0.32 (60% EtOAc/Hexanes); IR (thin film) 2919, 2853, 1716, 1153 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 8.0 Hz, 1H), 5.72 (d, *J* = 16.0 Hz, 1H), 5.47 (t, *J* = 7.0 Hz, 1H), 4.72 (s, 1H), 4.58 (d, *J* = 16.0 Hz, 1H), 4.32 (d, *J* = 12.5

Hz, 1H), 3.85 (m, 1H), 3.68 (s, 3H), 3.63 (m, 2H), 3.37-3.44 (m, 3H), 3.33 (s, 3H), 3.18-3.24 (m, 2H), 3.06 (m, 1H), 2.89 (m, 1H), 1.87 (s, 3H), 1.85 (s, 3H), 1.79 (s, 3H), 0.68 (bs, 1H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 173.64, 171.57, 156.71, 150.31, 150.06, 145.41, 144.66, 142.55, 138.07, 135.97, 135.13, 129.94, 129.60, 129.52, 129.48, 129.16, 128.80, 127.39, 121.42, 112.87, 112.82, 112.24, 76.42, 63.48, 61.30, 60.60, 55.74, 55.29, 50.62, 47.53, 47.07, 46.43, 45.87, 41.49, 33.18, 30.08, 21.09, 20.97; MS (ESI) calcd for $C_{43}H_{47}ClN_4O_{12}S_3$: 942; found [M+Li]: 949.



Lactam 3.22: To a solution of the Diels-Alder adduct **3.4** (20 mg, 0.022 mmol) in anhydrous THF (0.2 mL) was added samarium diiodide (0.1 M solution in THF, 0.45 mL, 0.045 mmol) at 0 ºC, until the reaction mixture stayed blue. After 15 min at 0 ºC the reaction was quenched with sat'd $NaHCO_3$. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried over Na_2SO_4. Solvent was removed *in vacuo* to afford the free lactam **3.22** in high purity (12 mg, 73%). R_f = 0.17 (EtOAc); $[\alpha]_D$ -21.26 (*c* 1.25, CH_2Cl_2), IR (thin film) 3239, 2940, 2866, 1682, 1652 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.64 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.81 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 2H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.48 (bs, 1H), 5.48 (d, *J* = 10.0 Hz, 1H), 4.56 (d, *J* = 15.5 Hz, 1H), 4.44 (d, *J* = 15.5 Hz, 1H),

4.04-4.11 (m, 1H), 3.95-4.02 (m, 3H), 3.80-3.86 (m, 1H), 3.69-3.71 (m, 2H), 3.60 (d, *J* = 7.0 Hz, 1H), 3.54 (s, 3H), 3.35 (s, 3H), 3.23 (t, *J* = 5.0 Hz, 1H), 3.01-3.05 (dt, *J* = 4.5, 14.0 Hz, 1H), 2.95 (dd, *J* = 7.5, 3.5 Hz, 1H), 2.83-2.88 (m, 1H), 2.15-2.19 (dd, *J* = 4.5, 16.0 Hz, 1H), 1.85 (s, 3H), 1.70-1.75 (m, 1H), 1.10-1.15 (m, 21H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 178.16, 154.02, 150.44, 149.68, 144.29, 137.77, 130.66, 129.79, 128.35, 120.10, 119.86, 115.25, 112.28, 112.05, 65.86, 65.47, 60.16, 55.72, 55.55, 53.42, 45.68, 44.46, 37.21, 36.26, 35.91, 21.17, 19.85, 18.31, 18.30, 12.25; HRMS (ESI) calculated for $C_{38}H_{55}N_3O_8SSi$ [M+H]: 742.3557, found: 742.3552.

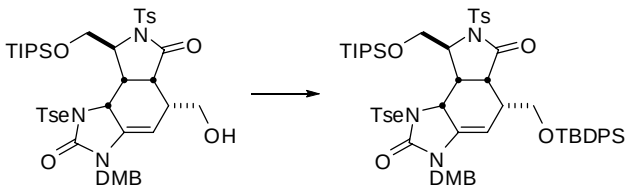


Initial Diels-Alder adduct 3.27a: To a mixture of dienophile **2.3** (24 mg, 0.057 mmol), diene **2.33** (68 mg, 0.14 mmol) and $LiClO_4$ (~1 mg, 0.01 mmol) in anhydrous benzene (0.5 mL) was added 2,6-lutidine (5 μL, 0.043 mmol). The reaction vial was sealed and heated to 90 °C. After 12 h reaction time, the reaction mixture was cooled to 20 °C and filtered to remove excess amount of unreacted diene **2.33**. The filtrate was concentrated *in vacuo* and purified by flash column (silica gel, 40 → 60% EtOAc/Hexanes) to yield the initial Diels-Alder adduct **3.27a** along with its regioisomer (41 mg, 81%). The inseparable mixture of regioisomers was taken onto the subsequent TBDPS protection

reaction, and the resulting TBDPS-protected products could be separated by column chromatography.

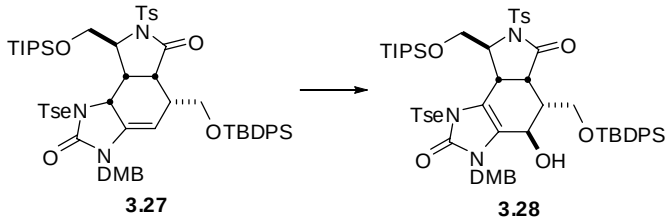
A pure sample of initial Diels-Alder adduct **3.27a** was obtained by the following procedure[92]: to a mixture of diene **2.33** (42 mg, 0.089 mmol) and cerium trichloride (11 mg, 0.044 mmol) in anhydrous benzene (0.50 mL) was added *i*PrMgCl (2.0 M in THF, 0.050 mL, 0.10 mmol) at 0 °C. The mixture was allowed to warm to 20 °C. After 20 min at 20 °C, a solution of dienophile **2.3** (38 mg, 0.089 mmol) in benzene (0.40 mL) was added to the reaction mixture and the reaction was heated to 80 °C for 96 h. Upon completion of the reaction time, the reaction was quenched with water (10 mL) and extracted with EtOAc (3 X 10 mL). The combined organics was washed with water and brine, and dried over Na_2SO_4. After solvent removal *in vacuo*, the crude product was subjected to column purification (Silica gel, 50 → 75% EtOAc/Hexanes) to afford the initial Diels-Alder adduct **3.27a** (15 mg, 19%) and the rearranged adduct **3.4** (14 mg, 18%). **3.27a**: R_f = 0.72 (EtOAc); $[\alpha]_D$ -84.7 (*c* 1.00, CH_2Cl_2); IR (thin film) 3519, 2940, 2858, 1726, 1675 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.92 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 1H), 4.83 (d, *J* = 15.5 Hz, 1H), 4.50 (t, *J* = 3.5 Hz, 1H), 4.31(m, 1H), 4.19-4.22 (m, 1H), 4.13-4.18 (dt, *J* = 5.5, 14.5 Hz, 1H), 4.09-4.12 (dd, *J* = 5.5, 10.5 Hz, 1H), 3.98 (dd, *J* = 2.5, 10.0 Hz, 1H), 3.78 (d, *J* = 15.5 Hz, 1H), 3.70-3.74 (m, 2H), 3.62-3.66 (m, 1H), 3.60 (s, 3H), 3.49-3.55 (m, 1H), 3.32 (s, 3H), 3.06-3.10 (m, 1H), 2.90-2.95 (m, 3H), 1.83-1.88 (m, 7H), 1.11-1.17 (m, 21H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 174.73, 158.50, 150.58, 149.73, 144.59,

144.54, 137.37, 137.23, 136.48, 129.90, 129.55, 129.16, 128.72, 119.63, 112.54, 111.51, 92.46, 66.09, 62.89, 60.35, 55.70, 55.47, 54.32, 52.63, 44.79, 44.65, 38.37, 36.52, 35.73, 21.06, 21.04, 18.21, 18.16, 12.18; HRMS (ESI) calculated for $C_{45}H_{61}N_3O_{10}S_2Si$ [M+Li]: 902.3728. Found: 902.3766.



TBDPS-protected initial adduct 3.27: To a solution of initial Diels-Alder adduct **3.27a** (33 mg mixture of **3.27a** and its regioisomer, 0.037 mmol) in CH_2Cl_2 was added triethylamine (8 μL, 0.055 mmol), followed by TBDPSCl (11 μL, 0.041 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at 20 °C for 12 h, and then concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 20 → 40% EtOAc/Hexanes) to afford the TBDPS silylether **3.27** as a colorless foam (25 mg, 60%): R_f = 0.74 (60% EtOAc/Hexanes); IR (thin film) 2940, 2858, 1726, 1680 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 8.02 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.75-7.77 (m, 4H), 7.21-7.28 (m, 6H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.81 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.59 (d, *J* = 8.0 Hz, 1H), 4.93 (d, *J* = 15.0 Hz, 1H), 4.49-4.53 (dd, *J* = 10.0, 8.5 Hz, 1H), 4.39 (t, *J* = 3.5 Hz, 1H), 4.36(m, 1H), 4.05-4.16 (m, 5H), 3.58 (s, 3H), 3.52-3.56 (m, 1H), 3.48 (d, *J* = 15.0 Hz, 1H), 3.39-3.43 (m, 1H), 3.32 (s, 3H), 3.22-3.25 (dd, *J* = 9.0, 3.5 Hz, 1H),

2.97-3.04 (m, 2H), 2.31 (m, 1H), 1.86 (s, 3H), 1.85 (s, 3H), 1.17 (s, 9H), 1.11-1.16 (m, 21H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 172.91, 158.39, 150.58, 149.67, 144.49, 144.20, 137.17, 137.11, 137.01, 136.01, 135.87, 134.06, 134.01, 129.92, 129.88, 129.87, 129.57, 129.14, 128.61, 128.23, 128.02, 127.99, 119.69, 112.38, 111.53, 93.22, 66.42, 63.78, 59.23, 55.68, 55.47, 54.03, 52.39, 44.70, 42.36, 39.52, 36.57, 36.32, 27.06, 21.05, 19.43, 18.23, 18.21, 18.17, 12.17; MS (MALDI): (M+H) 1134, (M+Na) 1156, (M+K) 1172; HRMS (ESI) calcd for $C_{61}H_{79}N_3O_{10}S_2Si_2$ [M+Li]: 1140.4905. Found: 1140.4898.



Allylic alcohol 3.28: To a stirred slurry of TBDPS silylether **3.27** (6.0 mg, 0.0053 mmol) and $MgSO_4$ (~50 mg) in anhydrous CH_2Cl_2 (0.30 mL) was added dimethyl dioxarane (DMDO, 0.07 M solution in acetone, 0.083 mL, 0.0058 mmol) at -78 °C. The reaction was stirred for 1h at -78 °C, then warmed to 20 °C and filtered. After concentration of the filtrate *in vacuo*, the crude product was subjected to column purification (silica gel, 40 → 60% EtOAc/Hexanes) to afford the allylic alcohol **3.28** as a colorless foam (5 mg, 83%): R_f = 0.44 (60% EtOAc/Hexanes); IR (thin film) 2925, 2858, 1737, 1690 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.69-7.75 (m, 6H), 7.61 (d, J = 8.0 Hz, 2H), 7.19-7.22 (m, 7H), 7.11 (dd, J = 8.0, 2.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 2H), 6.61 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 2H), 4.92 (d, J = 15.0 Hz, 1H), 4.83-4.87 (dd, J = 10.5, 9.0 Hz, 1H),

4.76 (d, *J* = 15.0 Hz, 1H), 4.69 (dt, *J* = 9.0, 3.0 Hz, 1H), 4.36-4.40 (m, 2H), 4.22-4.28 (m, 1H), 4.06-4.15 (m, 3H), 3.85 (dd, *J* = 7.0, 2.5 Hz, 1H), 3.80-3.85 (m, 1H), 3.69 (d, *J* = 3.0 Hz, 1H), 3.55 (s, 3H), 3.38 (s, 3H), 3.15 (dd, *J* = 6.5, 3.5 Hz, 1H), 2.92-2.96 (m, 1H), 2.07-2.13 (m, 1H), 1.89 (s, 3H), 1.88 (s, 3H), 1.13-1.17 (m, 21H), 1.11 (s, 9H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 172.41, 153.97, 150.06, 149.42, 144.92, 143.98, 137.71, 135.79, 135.76, 132.87, 132.66, 131.22, 130.33, 130.27, 129.78, 129.52, 127.51, 127.38, 121.94, 120.70, 115.12, 112.77, 112.13, 66.10, 65.18, 64.93, 63.96, 55.51, 55.42, 52.76, 45.70, 44.61, 41.58, 36.89, 34.74, 30.08, 27.02, 26.91, 21.09, 19.13, 18.18, 18.15, 12.11; HRMS (MALDI) calcd for $C_{61}H_{79}N_3O_{11}S_2Si_2$ [M+H]: 1150.4773, found: 1150.4745; calcd [M+Na]: 1172.4592, found 1172.4604.

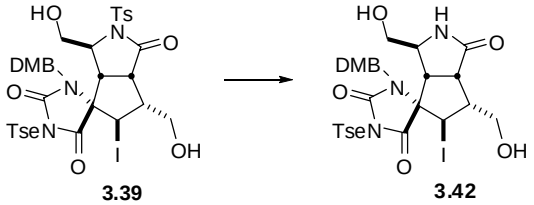
Iodospirohydantoin 3.37: To a slurry of allylic alcohol **2.35** (55.0 mg, 0.048 mmol) and $MgSO_4$ (~100 mg) in CH_2Cl_2 at -50 °C was added *N*-iodosuccinimide (13.0 mg, 0.058 mmol). The reaction was allowed to warm to 20 °C slowly and stirring was continued for 16 h. The reaction mixture was then filtered and the filtrate was concentrated *in vacuo*. Column purification (silica gel, 20 → 30% EtOAc/Hexanes) afforded the iodocyclopentane **3.37** as a colorless foam: 32.0 mg (52%): R_f = 0.39 (40% EtOAc:hexanes); $[\alpha]_D$ –25.8 (*c* 1.03, CH_2Cl_2); IR (thin film) 2935, 2858, 1716 cm^{-1}; ^{1}H-

NMR (500 MHz, benzene-d_6) δ 8.26 (d, J = 8.0 Hz, 2H), 7.97 (m, 2H), 7.87 (d, J =8.0 Hz, 2H), 7.83 (m, 2H), 7.48 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 2.0, 8.0 Hz, 1H), 7.20-7.29 (m, 6H), 6.84 (d, J =8.0 Hz, 2H), 6.77 (d, J =8.0 Hz, 2H), 6.38 (d, J =8.0 Hz, 1H), 5.85 (d, J = 16.0 Hz, 1H), 4.89 (s, 1H), 4.63 (d, J = 16.0 Hz, 1H), 4.60 (t, J = 10.0 Hz, 1H), 4.39 (d, J = 13.5 Hz, 1H), 4.25 (dd, J = 2.0, 11.0 Hz, 1H), 4.19 (dd, J = 4.0, 10.0 Hz, 1H), 4.14 (d, J = 11.0 Hz, 1H), 3.89 (m, 1H), 3.81 (d, J = 8.5 Hz, 1H), 3.63 (s, 3H), 3.56-3.61 (m, 2H), 3.43 (m, 1H), 3.31 (s, 3H), 3.24 (m, 1H), 2.94 (m, 1H), 1.88 (s, 3H), 1.85 (s, 3H), 1.21 (s, 9H), 0.91-0.99 (m, 21H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 174.48, 171.74, 156.60, 150.30, 150.01, 144.84, 144.68, 136.42, 136.18, 136.01, 135.70, 133.78, 133.62, 130.39, 129.81, 129.76, 129.55, 129.10, 129.06, 128.20, 128.01, 127.95, 127.82, 122.14, 113.79, 112.18, 77.86, 65.42, 61.42, 61.24, 55.68, 55.32, 50.56, 50.36, 48.59, 48.44, 45.84, 33.25, 30.08, 26.99, 25.96, 21.06, 21.02, 19.40, 18.11, 18.05, 12.11; HRMS (MALDI) calcd for $C_{61}H_{78}IN_3O_{11}S_2Si_2$ [M+Na]: 1298.3559; found: 1298.3560.

3.37 **3.39**

Iodocyclopentane 3.39: To a solution of iodocyclopentane **3.37** (11.0 mg, 0.0086 mmol) in THF (0.20 mL) was added HF·pyridine (70%, 50 μL, excess) at 20 °C. After 21 h, the reaction was quenched with saturated $NaHCO_3$ (1 mL) and H_2O (3 mL) and extracted with EtOAc (3 X 10 mL). The combined organic layers were washed with brine and

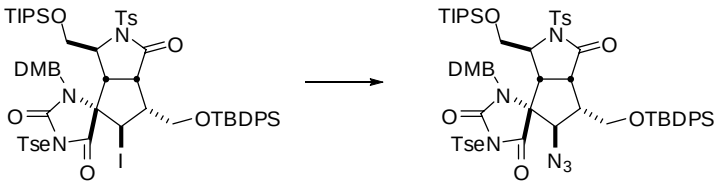
further dried over Na_2SO_4. After removal of solvent, the crude product was purified by flash column chromatography (silica gel, 60 → 80% EtOAc/hexanes) to give alcohol **3.39** as a colorless film (5.6 mg, 74%): R_f = 0.22 (60% EtOAc/hexanes); $[\alpha]_D$ –35.2 (*c* 1.00, CH_2Cl_2); IR (thin film) 3493, 2925, 1711 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* =8.0 Hz, 2H), 7.41 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.69 (d, *J* = 8.0 Hz, 2H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.62 (d, *J* = 16.0 Hz, 1H), 4.77 (s, 1H), 4.72 (d, *J* = 13.0 Hz, 1H), 4.47 (d, *J* = 16.0 Hz, 1H), 4.02 (m, 1H), 3.91 (m, 2H), 3.73 (s, 3H), 3.66-3.72 (m, 2H), 3.48-3.52 (m, 1H), 3.43 (d, *J* = 9.0 Hz, 1H), 3.35 (s, 3H), 3.18-3.23 (m, 1H), 3.10 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.06 (t, *J* = 9.0 Hz, 1H), 2.96 (m, 1H), 1.86 (s, 3H), 1.77 (s, 3H), 1.36 (s, 1H), 1.06 (s, 1H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 175.30, 174.26, 169.91, 156.60, 150.37, 150.09, 145.27, 144.82, 135.90, 135.27, 130.20, 129.90, 129.51, 129.28, 128.80, 128.20, 127.56, 122.29, 113.73, 112.38, 77.66, 63.70, 61.60, 59.93, 59.08, 55.71, 55.37, 50.78, 49.39, 49.35, 47.45, 45.93, 33.12, 31.82, 30.09, 26.33, 22.91, 21.06, 21.05, 20.41, 14.21, 14.08; HRMS (ESI) calcd for $C_{36}H_{40}IN_3O_{11}S_2$ [M+Li]: 888.1309; found: 888.1329.



3.39 **3.42**

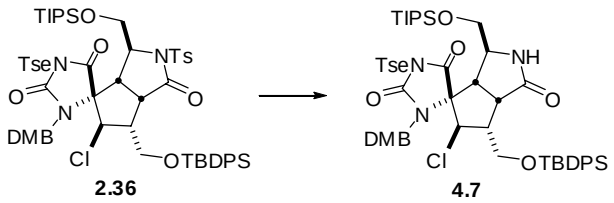
Lactam 3.42: To a solution of iodocyclopentane **3.39** (3.7 mg, 0.0042 mmol) in THF (0.10 mL) was added SmI_2 (0.1 M solution in THF, 130 μL, 0.013 mmol) at 0 °C. After

30 min, a further portion of SmI_2 (0.10 mL) was added. The blue reaction mixture was stirred at 20 °C for 10 min. The reaction was then quenched with saturated $NaHCO_3$ (2 mL) and extracted with EtOAc (3 X 10 mL). The combined organic layers were washed sequentially with water and brine, and then dried over Na_2SO_4. Removal of solvent afforded lactam **3.42** as a colorless film and of sufficient purity for subsequent reactions (3.0 mg, 99%): R_f = 0.14 (EtOAc); $[\alpha]_D$ +23.5 (*c* 1.00, CH_2Cl_2); IR (thin film) 3345, 2925, 1711 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 2.0 Hz, 1H),7.12 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.61 (d, *J* = 8.0 Hz, 1H), 5.31 (s, 1H), 4.97 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 12.5 Hz, 1H), 4.42 (bs, 1H), 4.16 (d, *J* = 12.5 Hz, 1H), 4.06 (d, *J* = 16.0 Hz, 1H), 3.95 (m, 1H), 3.74 (s, 3H), 3.60-3.65 (m, 1H), 3.51-3.56 (m, 1H), 3.38 (s, 3H), 3.33 (t, *J* = 4.5 Hz, 1H), 3.18 (d, *J* = 8.5 Hz, 1H), 3.10-3.15 (m, 3H), 2.98 (m, 1H), 2.90 (m, 1H), 2.68 (t, *J* = 8.5 Hz, 1H), 1.85 (s, 3H), 1.32 (bs, 1H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 178.02, 174.52, 156.83, 150.45, 150.06, 144.83, 135.93, 130.05, 129.88, 128.73, 128.39, 127.37, 121.51, 113.31, 112.27, 77.35, 65.16, 59.93, 59.18, 55.46, 50.79, 48.46, 48.16, 47.40, 45.31, 33.04, 30.08, 26.91, 21.04, 14.21, 14.15, 14.08; HRMS (MALDI) calcd for $C_{29}H_{34}IN_3O_9S$ [M+H]: 728.1139, found: 728.1118.



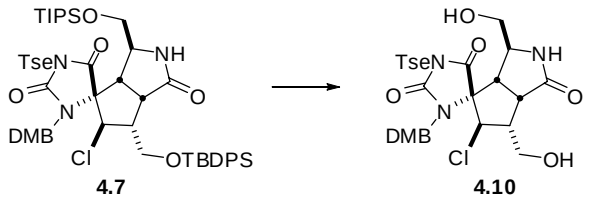
3.37 **3.46**

Azidocyclopentane 3.46: To a mixture of iodocyclopentane **3.37** (10 mg, 0.0078 mmol) and NaN_3 (34 mg, 0.52 mmol) in a dry vial was added anhydrous DMF (0.40 mL). The reaction vessel was purged with nitrogen and sealed with a teflon cap and then heated to 105 °C. After 12 h, the reaction was cooled to 20 °C, H_2O (5 mL) was added, and the mixture was extracted with EtOAc (3 X 10 mL). The combined organics were washed with brine and then dried over Na_2SO_4. Concentration *in vacuo* and column purification (silica gel, 25% EtOAc/Hexanes) afforded the azidocyclopentane **3.46** as a colorless film: 7.0 mg (75%): R_f = 0.38 (6:4-hexanes:EtOAc); $[\alpha]_D$ –25.8 (*c* 1.00, CH_2Cl_2); IR (thin film) 2926, 2113, 1716, 1113 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ 8.21 (d, *J* = 8.0 Hz, 2H), 7.91 (m, 2H), 7.87 (d, *J* =8.0 Hz, 2H), 7.76 (m, 2H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.42 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.19-7.27 (m, 6H), 6.84 (d, *J* =8.0 Hz, 2H), 6.77 (d, *J* =8.0 Hz, 2H), 6.50 (d, *J* =8.0 Hz, 1H), 5.94 (d, *J* = 16.0 Hz, 1H), 4.87 (s, 1H), 4.74 (d, *J* = 16.0 Hz, 1H), 4.60 (dd, *J* = 6.0, 11.0 Hz, 1H), 4.32 (d, *J* = 11.0 Hz, 1H), 4.17-4.22 (m, 2H), 4.07 (d, *J* = 9.5 Hz, 1H), 3.67 (s, 3H), 3.55-3.62 (m, 4H),3.36(m, 1H), 3.35 (s, 3H), 3.20 (m, 1H), 2.91 (m, 1H), 1.87 (s, 3H), 1.84 (s, 3H), 1.19 (s, 9H), 0.88-0.94 (m, 21H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 173.66, 172.29, 156.93, 150.72, 150.20, 144.88, 144.67, 136.31, 136.19, 135.84, 135.78, 133.64, 133.52, 130.19, 129.80, 129.53, 129.09, 129.01, 128.21, 128.02, 127.82, 127.63, 120.86, 112.72, 112.60, 75.24, 66.59, 65.29, 62.29, 61.31, 55.76, 55.44, 50.48, 47.78, 47.37, 47.20, 45.80, 33.35, 30.08, 26.95, 21.07, 21.01, 19.30, 18.06, 18.00, 12.04; HRMS (ESI) calcd for $C_{61}H_{78}N_6O_{11}S_2Si_2$ [M+Li]: 1197.4869; found: 1197.4800.



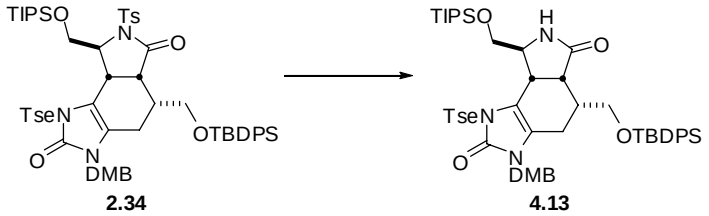
Lactam 4.7: To a solution of the chlorocyclopentane **2.36** (30 mg, 0.025 mmol) in anhydrous THF (0.20 mL) was added samarium diiodide (0.1 M solution in THF) at 0 ºC, until the reaction mixture remained blue (about 1.5 mL, 0.15 mmol). The reaction was warmed to 20 °C and stirred for 30 min. Then the reaction was quenched with sat'd $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 X 10 mL). The combined organic layer was washed with water and brine, and dried over Na_2SO_4. After solvent removal *in vacuo*, the crude product was subjected to column purification (Silica gel, 20 → 30% EtOAc/Hexanes) to afford lactam **4.7** (25 mg, 96%): R_f = 0.64 (60% EtOAc/Hexanes); $[\alpha]_D$ +25.1 (*c* 1.00, CH_2Cl_2); IR (thin film) 2971, 1738, 1217 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.96 (m, 2H), 7.90 (m, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.22-7.33 (m, 7H), 6.95 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.45 (d, *J* = 8.0 Hz, 2H), 5.51 (s, 1H), 5.04 (d, *J* = 15.5 Hz, 1H), 4.60 (d, *J* =11.0 Hz, 1H), 4.42 (d, *J* = 15.5 Hz, 1H), 4.40 (t, *J* = 3.0 Hz, 1H), 4.27 (dd, *J* = 3.0, 10.0 Hz, 1H), 3.67 (m, 1H), 3.65 (s, 3H), 3.46-3.62 (m, 6H), 3.41 (dd, *J* = 2.0, 8.0 Hz, 1H), 3.34 (s, 3H), 3.13-3.19 (m, 1H), 3.01-3.06 (m, 1H), 1.85 (s, 3H), 1.26 (s, 9H), 1.04-1.06 (m, 21H); ^{13}C-NMR (125 MHz, benzene-d_6) δ 175.35, 173.11, 157.15, 150.40, 149.82, 144.61, 136.21, 136.15, 136.02, 133.90, 133.50, 129.84, 129.81, 129.80, 129.62, 128.88, 128.20, 127.99, 120.40, 112.51, 111.84, 76.60, 66.74, 59.90, 59.38, 55.70, 55.28, 55.25, 50.75, 48.08,

47.97, 45.37, 44.31, 33.24, 30.08, 27.09, 21.04, 19.54, 18.09, 12.03; HRMS (ESI) calculated for $C_{54}H_{72}ClN_3O_9SSi_2$ [M+Li]: 1036.4376, found: 1036.4366.



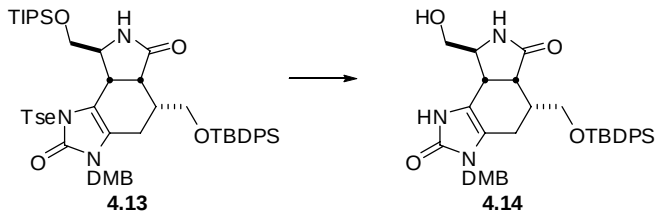
Diol 4.10: To a solution of iodocyclopentane **4.7** (24 mg, 0.0233 mmol) in THF (0.40 mL) was added HF·pyridine (70%, 100 μL, excess) at 20 °C. The reaction mixture was stirred vigorously at 20 °C for 20 h. After the reaction time, the reaction was quenched with saturated $NaHCO_3$ (2 mL) and H_2O (6 mL) and extracted with EtOAc (3 X 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of solvent, the crude product was purified by flash column chromatography (silica gel, 80% EtOAc/hexanes to EtOAc) to give diol **4.10** as a colorless film (15 mg, 99%): R_f = 0.15 (EtOAc); $[\alpha]_D$ +29.1 (*c* 1.00, CH_2Cl_2); IR (thin film) 3383, 1713, 1262 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* =8.0 Hz, 2H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.61 (s, 1H), 4.77 (d, *J* = 16.0 Hz, 1H), 4.44-4.48 (m, 2H), 3.98-4.03 (m, 1H), 3.79-3.94 (m, 3H), 3.86 (s, 6H), 3.65 (s, 1H), 3.44-3.54 (m, 4H), 3.30 (t, *J* = 8.5 Hz, 1H), 3.17 (d, *J* = 8.5 Hz, 1H), 3.07 (m, 1H), 2.47 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 178.57, 173.12, 171.43, 156.99, 149.48, 149.47, 149.03, 149.01, 145.82, 135.25, 130.43, 129.05, 128.61, 120.43, 111.52, 111.27, 76.42, 65.57, 60.65, 59.02, 57.91, 56.29, 56.15, 56.08, 51.34, 47.36,

46.67, 46.08, 45.62, 33.31, 21.95, 21.31, 14.44; HRMS (ESI) calcd for $C_{29}H_{34}ClN_3O_9S$ [M+Li]: 642.1864; found: 642.1853.



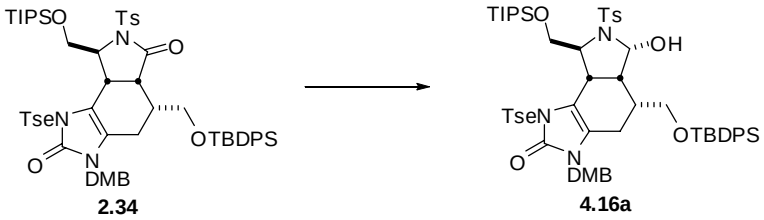
Lactam 4.13: To a solution of the TBDPS-protected Diels-Alder adduct **2.34** (40 mg, 0.035 mmol) in anhydrous THF (0.30 mL) was added samarium diiodide (0.1 M solution in THF, excess) at 0 °C, until the reaction mixture stayed blue. After 30 min at 0 °C the reaction was quenched with sat'd $NaHCO_3$. The mixture was extracted with EtOAc (2 X 10 mL). The organic layer was washed with water and brine, and dried over Na_2SO_4. Solvent was removed *in vacuo* to afford the free lactam **4.13** in high purity (36 mg, 100%): R_f = 0.29 (EtOAc); $[\alpha]_D$ -29.9 (*c* 1.20, CH_2Cl_2); IR (thin film) 2929, 2864, 1693, 1657 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.78-7.83 (m, 4H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.23-7.27 (m, 6H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.90 (bs, 1H), 6.77 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 2H), 6.53 (d, *J* = 8.0 Hz, 1H), 4.56 (dd, *J* = 10.0, 8.5 Hz, 1H), 4.51 (d, *J* = 15.5 Hz, 1H), 4.37 (d, *J* = 15.5 Hz, 1H), 4.33 (dd, *J* = 10.0, 6.0 Hz, 1H), 4.12 (m, 1H), 3.95 (m, 2H), 3.65 (m, 2H), 3.54 (d, *J* = 8.0 Hz, 1H), 3.51 (s, 3H), 3.37 (s, 3H), 3.17 (t, *J* = 5.5 Hz, 1H), 3.10 (dt, *J* = 14.5, 5.0 Hz, 1H), 2.97 (dd, *J* = 7.5, 3.5 Hz, 1H), 2.48 (m, 1H), 2.31 (m, 1H), 2.17 (bs, 1H), 1.89 (s, 3H), 1.20 (s, 9H), 1.14 (m, 21H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 176.86, 153.73, 150.38, 149.50, 143.92, 137.62,

135.96, 135.88, 134.16, 134.12, 130.56, 129.96, 129.50, 128.22, 128.05, 127.84, 127.78, 119.77, 119.12, 115.84, 112.15, 111.72, 65.71, 65.68, 59.33, 55.55, 55.43, 53.19, 44.28, 40.34, 38.67, 36.42, 35.11, 27.13, 21.10, 20.83, 19.46, 18.21, 12.14; HRMS (ESI) calcd for $C_{54}H_{73}N_3O_8SSi_2$ [M+Li] 986.4817; found [M+Li] 986.4820.



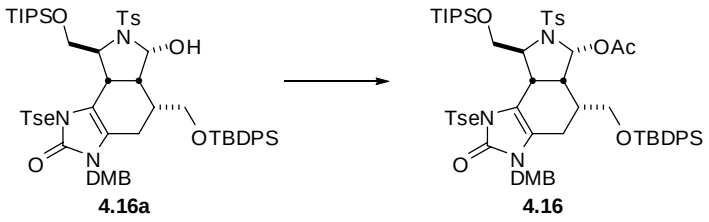
Alcohol 4.14: To a solution of lactam **4.13** (34 mg, 0.035 mmol) in THF was added lithium aluminum hydride (LAH, 10 mg, 0.26 mmol) at 0 °C. The reaction mixture was warmed to 20 °C and stirred for 3 h. Then the reaction mixture was cooled to 0 °C and treated with water (2 mL) and 8% NaOH solution (1 mL). The resulting mixture was partitioned between water (10 mL) and methylene chloride (3 X 10 mL). The combined organic layer was washed with water and brine, and dried over Na_2SO_4. After solvent removal *in vacuo*, the crude product was subjected to column purification (silica gel, 10 → 20% MeOH/CH_2Cl_2) to afford alcohol **4.14** as a colorless foam (19 mg, 86%): R_f = 0.10 (8% MeOH/CH_2Cl_2); $[\alpha]_D$ -35.2 (*c* 1.00, CH_2Cl_2); IR (thin film) 3231, 2931, 1671, 1262 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 10.26 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 4H), 7.35-7.43 (m, 6H), 6.69-6.77 (m, 3H), 6.29 (s, 1H), 4.78 (d, *J* = 15.5 Hz, 1H), 4.54 (d, *J* = 15.5 Hz, 1H), 4.45 (bs, 1H), 4.14 (m, 1H), 4.07 (m, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.50 (s, 3H), 3.17 (d, *J* = 6.5 Hz, 1H), 2.94 (d, *J* = 6.5 Hz, 1H), 2.46 (d, *J* = 12.5 Hz, 1H),

2.16 (m, 2H), 2.04 (bs, 1H), 1.29 (s, 1H), 1.04 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 176.68, 154.92, 149.45, 148.80, 135.80, 135.77, 133.97, 133.87, 129.95, 129.74, 128.07, 127.94, 120.20, 119.60, 115.41, 111.45, 110.85, 65.09, 64.52, 59.26, 56.16, 56.09, 44.53, 39.84, 37.93, 35.66, 29.97, 27.12, 20.63, 19.49; MS (MALDI) unit mass $C_{36}H_{43}N_3O_6Si$: 641, found [M+H] 642, [M+Na] 664, [M+K] 680.



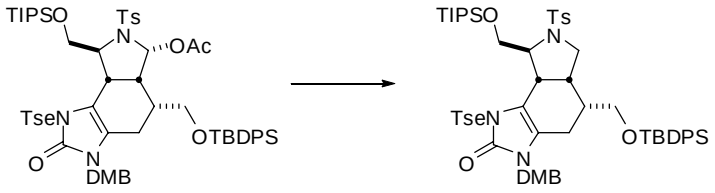
Aminal 4.16a: To a solution of TBDPS-protected Diels-Alder adduct **2.34** (202 mg, 0.178 mmol) in CH_2Cl_2 (1.2 mL) at -78 °C was added DIBAl-H (0.13 mL DIBAl-H in 0.6 mL CH_2Cl_2, 0.712 mmol). The reaction mixture was stirred at -78 °C for 2 h. After 2 h, the reaction was quenched with Rochelle's salt solution (~ 5 mL). The reaction mixture was warmed to 20 °C and stirred vigorously for 8 h, after which the mixture was transferred into a separation funnel and extracted with CH_2Cl_2. The organic layer was washed with brine and dried further over Na_2SO_4. After removal of solvent *in vacuo*, aminal **4.16a** was obtained in high purity as a foam (202mg, 99%): R_f = 0.26 (60% EtOAc/Hexanes); $[\alpha]_D$ -22.9 (*c* 1.01, CH_2Cl_2); IR (thin film) 2938, 2866, 1692 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.73-7.77 (m, 4H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.23-7.26 (m, 6H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.87 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 2H), 5.17 (dd, *J* =

6.0, 2.5 Hz, 1H), 4.85 (d, *J* = 15.5 Hz, 1H), 4.32 (dd, *J* = 10.0, 3.5 Hz, 1H), 4.02-4.11 (m, 3H), 3.89 (d, *J* = 15.5 Hz, 1H), 3.84 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.73-3.80 (m, 3H), 3.63 (bd, *J* = 10.0 Hz, 1H), 3.61 (s, 3H), 3.41 (s, 3H), 3.31 (d, *J* = 2.5 Hz, 1H), 2.94 (m, 1H), 2.83 (m, 1H), 2.33-2.37 (dd, *J* = 15.5, 4.5 Hz, 1H), 2.19 (s, 3H), 1.93 (bs, 1H), 1.82 (s, 3H), 1.54-1.59 (m, 1H), 1.19-1.23 (m, 21H), 1.17 (s, 9H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 153.46, 150.57, 149.62, 144.23, 143.98, 137.92, 135.93, 135.90, 135.44, 134.02, 133.74, 130.49, 130.05, 129.62, 129.58, 128.21, 128.07, 128.05, 127.83, 126.80, 119.60, 117.61, 114.50, 112.24, 111.92, 84.53, 66.16, 65.99, 64.07, 55.83, 55.55, 52.61, 45.43, 44.25, 37.58, 36.73, 36.20, 27.01, 21.58, 21.05, 20.12, 19.33, 18.28, 12.16, 12.13; MS (ESI) calcd for $C_{61}H_{81}N_3O_{10}S_2Si_2$ [M+H] 1136; found [M+H] 1136.



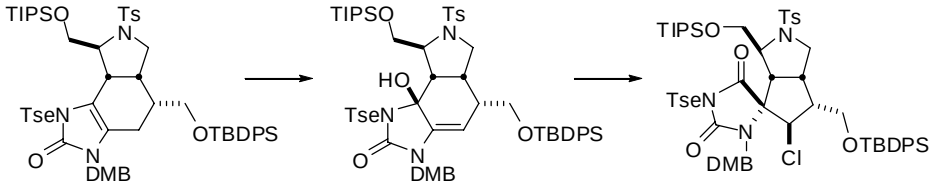
Acetate 4.16: To a solution of aminal **4.16a** (202 mg, 0.178 mmol) in CH_2Cl_2 (1.8 mL) at 0 ºC was added pyridine (0.43 mL, 5.34 mmol), followed by acetic anhydride (0.34 mL, 3.56 mmol). The reaction mixture was warmed to 20 °C and stirred for 12 h. Upon completion of the reaction time, volatile compounds in the reaction mixture were removed *in vacuo*. Purification of the residue by silica gel column (60% EtOAc/ Hexanes) afforded the acetate **4.16** as a colorless foam (206 mg, 98%): R_f = 0.26 (60% EtOAc/Hexanes); $[\alpha]_D$ -11.5 (*c* 1.03, CH_2Cl_2); IR (thin film) 2936, 2866, 1745, 1694

cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.71 (d, *J* = 8.5 Hz, 2H), 7.67 (m, 2H), 7.61-7.64 (m, 4H), 7.21-7.25 (m, 6H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.63-6.66 (m, 4H), 4.93 (d, *J* = 15.5 Hz, 1H), 4.37 (dd, *J* = 10.0, 3.0 Hz, 1H), 4.08-4.18 (m, 3H), 3.84-3.93 (m, 3H), 3.73 (d, *J* = 15.5 Hz, 1H), 3.71 (bd, *J* = 7.5 Hz, 1H), 3.66 (m, 2H), 3.62 (s, 3H), 3.42 (s, 3H), 3.06 (m, 1H), 2.94 (m, 1H), 2.33-2.37 (dd, *J* = 16.0, 4.5 Hz, 1H), 2.15 (s, 3H), 1.98 (bs, 1H), 1.84-1.86 (m, 4H), 1.75 (s, 3H), 1.21-1.23 (m, 21H), 1.10 (s, 9H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 169.75, 153.47, 150.59, 149.57, 144.15, 144.04, 137.93, 135.80, 135.67, 134.87, 133.69, 133.48, 130.38, 130.09, 130.03, 129.70, 129.65, 128.21, 128.04, 127.82, 127.06, 119.50, 117.68, 114.30, 112.16, 111.53, 82.42, 66.39, 65.65, 65.30, 55.78, 55.52, 52.56, 44.27, 44.16, 37.55, 36.89, 36.25, 26.90, 21.52, 21.15, 21.04, 20.08, 19.30, 18.28, 18.27, 12.19; HRMS (ESI) calcd for $C_{63}H_{83}N_3O_{11}S_2Si_2$ [M+H] 1178.5086; found [M+H] 1178.5101.



Ts-protected pyrrolidine 4.17: To a solution of acetate **4.16** (206 mg, 0.175 mmol) in CH_2Cl_2 (1.8 mL) at -50 ºC was added triethylsilane (0.42 mL, 2.62 mmol), followed by borontrifluoride etherate ($BF_3{\cdot}OEt_2$, 0.10 mL, ~0.70 mmol) (The solution changed color from light yellow to orange-pink after addition of $BF_3{\cdot}OEt_2$). The reaction mixture was stirred for 7 h at -50 ºC. Upon completion of the reaction, water (20 mL) was added at -

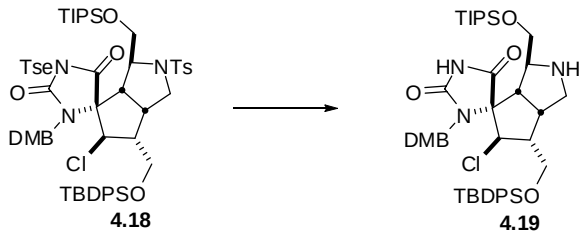
50 °C to quench the reaction. After warming up to 20 °C, the reaction mixture was extracted with CH_2Cl_2 (3 X 15 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Removal of solvents *in vacuo* afforded pyrrolidine **4.17** in sufficient purity for the next step (196 mg, 100%): R_f = 0.30 (60% EtOAc/Hexanes); $[\alpha]_D$ -20.8 (*c* 1.00, CH_2Cl_2); IR (thin film) 2945, 2863, 1696, 1655 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.67-7.69 (m, 4H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.26-7.28 (m, 6H), 7.04 (d, *J* = 2.0 Hz, 1H), 6.83 (m, 3H), 6.66 (m, 3H), 4.86 (d, *J* = 15.5 Hz, 1H), 4.31 (dd, *J* = 9.5, 3.5 Hz, 1H), 4.11-4.17 (m, 2H), 3.81-3.94 (m, 5H), 3.60 (s, 3H), 3.55 (m, 1H), 3.47-3.51 (m, 1H), 3.41 (s, 3H), 3.33-3.35 (m, 2H), 3.02 (t, *J* = 10.0 Hz, 1H), 2.97 (m, 1H), 2.76 (m, 1H), 2.19 (s, 3H), 1.99 (m, 1H), 1.83 (s, 3H), 1.75 (bs, 1H), 1.60-1.66 (m, 1H), 1.23-1.26 (m, 21H), 1.14 (s, 9H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 153.67, 150.62, 149.65, 143.91, 143.70, 138.02, 135.93, 135.91, 135.86, 135.85, 134.35, 133.56, 133.51, 130.61, 130.22, 130.16, 129.61, 129.33, 128.20, 128.05, 128.04, 128.02, 127.86, 127.83, 127.18, 119.46, 116.55, 114.59, 112.21, 111.90, 66.75, 66.59, 64.73, 55.84, 55.55, 52.60, 47.34, 44.17, 38.42, 37.86, 36.51, 36.35, 27.01, 26.98, 21.51, 21.01, 19.29, 19.02, 18.30, 18.27, 12.24; HRMS (ESI) calcd for $C_{61}H_{81}N_3O_9S_2Si_2$ [M+Li] 1126.5113; found [M+Li] 1126.5116.



Chlorocyclopentane 4.18: To a mixture of pyrrolidine **4.17** (196 mg, 0.175 mmol) and $MgSO_4$ (~200 mg) in CH_2Cl_2 (9.0 mL) at -60 ºC was added freshly prepared DMDO (~0.08 M in acetone, 2.6 mL, 0.21 mmol). The reaction mixture was stirred for two hours at -50 ºC. After 2 h, the reaction was quenched with 30 μL dimethylsulfide at -50 ºC. The reaction mixture was warmed to 20 °C and filtered to remove $MgSO_4$. Intermediate allylic alcohol **4.18a** was obtained after removal of solvents and was used directly for next step.

A mixture of alcohol **4.18a** (199 mg, 0.175 mmol) and $MgSO_4$ (~200 mg) in CH_2Cl_2 (16.0 mL) was cooled to -60 ºC and to this cooled slurry was added cyclohexene (90 μL, 0.875 mmol) and chloramine-T (80 mg, 0.35 mmol). The reaction mixture was allowed to warm to 20 °C slowly and stirred for 12 h. The reaction mixture was then partitioned between water and methylene chloride, and the combined organics were washed with brine and dried over Na_2SO_4. Column purification (silica gel, 25 → 30% EtOAc/Hexanes) after removal of solvents afforded chlorocyclopentane **4.18** as colorless foam (107 mg, 52% over two steps): R_f = 0.50 (40% EtOAc/Hexanes); $[\alpha]_D$ -17.7 (*c* 0.967, CH_2Cl_2); IR (thin film) 2937, 2861, 1774, 1715 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.87 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.68-7.72 (m, 4H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.31 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.21-7.28 (m, 6H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.49 (d, *J* = 8.0 Hz, 1H), 5.51 (d, *J* = 16.5 Hz, 1H), 4.78 (d, *J* = 16.5 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.52 (s, 1H), 4.22 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.95 (m, 1H), 3.83-3.88 (m, 3H), 3.72-3.80 (m, 3H), 3.69 (s, 3H), 3.56 (m, 1H), 3.34-3.41 (m, 2H), 3.32 (s, 3H), 3.23 (m, 1H), 3.12 (m, 1H), 1.90 (s, 3H), 1.85 (s, 3H),

1.16 (s, 9H), 0.99-1.03 (m, 21H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 173.68, 156.90, 150.28, 149.62, 144.51, 143.10, 138.14, 136.21, 136.04, 135.97, 133.31, 133.04, 130.35, 130.07, 130.06, 129.80, 129.77, 129.65, 129.38, 129.03, 128.22, 128.03, 127.84, 127.64, 127.57, 127.03, 126.65, 120.65, 112.49, 111.98, 76.33, 65.82, 62.84, 61.68, 59.27, 55.70, 55.28, 54.01, 53.21, 51.19, 50.18, 46.84, 45.49, 43.56, 33.42, 30.10, 27.06, 21.06, 20.97, 19.31, 18.17, 18.12, 12.07; HRMS (ESI) calcd for $C_{61}H_{80}ClN_3O_{10}S_2Si_2$ [M+Li] 1176.4672; found [M+Li] 1176.4744.



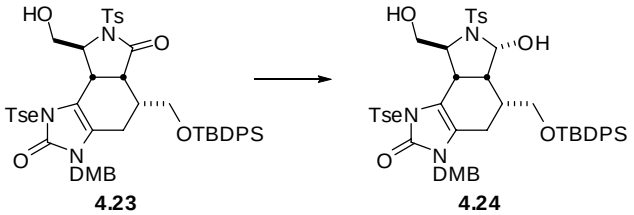
Pyrrolidine 4.19: To a solution of cyclopentane **4.18** (107 mg, 0.0914 mmol) in THF (1.0 mL) at -78 ºC was added 3.8 mL of freshly prepared sodium naphthalenide solution* (0.115 M, 0.457 mmol) dropwise. The reaction mixture was stirred at -78 ºC for 20 min. The reaction was quenched with pH 7 buffer at -78 ºC. After warming up to 20 °C, the reaction mixture was partitioned between water (20 mL) and EtOAc (2 X 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Column purification (silica gel, 30% EtOAc/Hexanes) after removal of solvents afforded pyrrolidine **4.19** (61 mg, 80%): R_f = 0.39 (40% EtOAc/Hexanes); IR (thin film) 3268, 2944, 2865, 1725 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.72-7.74 (m, 4H), 7.31 (d,

J = 2.0 Hz, 1H), 7.23-7.26 (m, 7H), 7.04 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 4.86 (d, *J* = 15.5 Hz, 1H), 4.75 (d, *J* = 15.5 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 3.93 (m, 1H), 3.75 (m, 1H), 3.61 (s, 3H), 3.40 (s, 3H), 3.34-3.39 (m, 2H), 3.24 (m, 1H), 3.21 (m, 2H), 2.96 (t, *J* = 10.5 Hz, 1H), 2.90 (m, 1H), 2.77 (dd, *J* = 8.5, 2.0 Hz, 1H), 1.16 (s, 9H), 1.02-1.04 (m, 21H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 174.59, 158.18, 150.15, 149.48, 135.95, 135.93, 133.57, 133.25, 130.79, 130.08, 130.02, 128.20, 128.01, 127.82, 120.65, 112.76, 111.69, 77.64, 63.98, 62.91, 62.11, 60.89, 59.36, 55.51, 55.26, 50.20, 45.72, 45.56, 44.93, 43.03, 30.83, 30.08, 27.12, 27.04, 19.34, 19.23, 18.09, 18.05, 18.04, 13.65, 12.05; HRMS (MALDI) calcd for $C_{45}H_{64}ClN_3O_6Si_2$ [M+H] 834.4100; found [M+H] 834.4108.

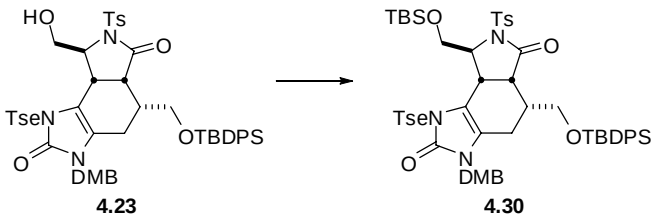
* Na naphthalenide preparation: to a solution of naphthalene (117 mg, 0.913 mmol) in 8.0 mL anhydrous THF was added excess amount of sodium. The mixture was sonicated for 15 min and then stirred for 2 h at 20 °C to give a deep green solution.

Alcohol 4.23: To a solution of Diels-Alder adduct **2.34** (19 mg, 0.0167 mmol) in THF at (0.80 mL) -50 ºC was added TBAF (1.0 M in THF, 17 µL, 0.017 mmol). The reaction mixture was stirred for 2 h at -50 ºC. After 2 h, the reaction was quenched with pH 7

buffer at -50 °C. After warming up to 20 °C, the reaction mixture was partitioned between water and EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Column purification (silica gel, 60 → 80% EtOAc/Hexanes) after removal of solvents afforded alcohol **4.23** (15 mg, 94%): R_f = 0.06 (60% EtOAc/Hexanes); $[\alpha]_D$ -50.0 (*c* 1.49, CH_2Cl_2); IR (thin film) 3300, 2930, 1734, 1684, 1653 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.81 (d, *J* = 8.5 Hz, 2H), 7.71-7.74 (m, 6H), 7.21-7.25 (m, 6H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.77 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 4H), 6.60 (d, *J* = 8.0 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.37 (dd, *J* = 8.5, 4.0 Hz, 1H), 4.32 (m, 1H), 4.12-4.18 (m, 3H), 4.04-4.10 (m, 2H), 3.91 (m, 1H), 3.62 (m, 1H), 3.57 (s, 3H), 3.47 (d, *J* = 6.0 Hz, 1H), 3.38 (s, 3H), 3.18 (m, 2H), 2.77 (dd, *J* = 6.5, 2.0 Hz, 1H), 2.35 (m, 1H), 1.93 (s, 3H), 1.90-1.93 (m, 2H), 1.85 (s, 3H), 1.13 (s, 9H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 172.85, 153.93, 150.51, 149.59, 144.72, 144.45, 137.14, 135.91, 135.86, 133.94, 133.84, 130.18, 130.05, 130.03, 129.86, 129.43, 128.22, 128.02, 127.99, 127.84, 120.45, 119.43, 114.41, 112.21, 111.41, 65.01, 64.15, 63.29, 55.68, 55.43, 53.80, 44.37, 41.56, 37.57, 35.94, 34.41, 27.02, 21.20, 21.08, 20.11, 19.38; HRMS (ESI) calcd for $C_{52}H_{59}N_3O_{10}S_2Si$ [M+H] 978.3489; found [M+H] 978.3446.

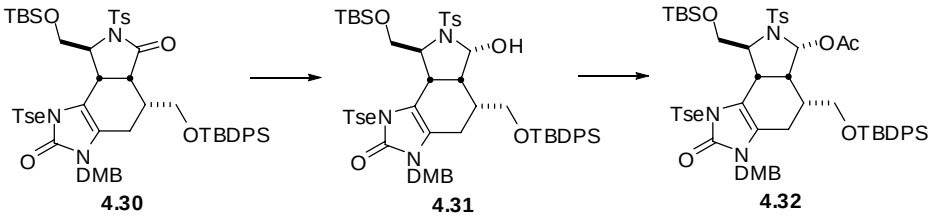


Diol 4.24: To a solution of alcohol **4.23** (157 mg, 0.160 mmol) in CH_2Cl_2 (1.0 mL) at -78 °C was added DIBAl-H (0.14 mL DIBAl-H in 0.6 mL CH_2Cl_2, 0.80 mmol). The reaction was stirred at -78 °C for 5 h, and then quenched with Rochelle's salt solution (5 mL) at -78 °C. The reaction mixture was allowed to warm to 20 °C and stirred vigorously for 4 h. Then the mixture was transferred into a separation funnel and extracted with CH_2Cl_2 (3 X 10 mL). The combined organics were washed with brine and dried over Na_2SO_4. After removal of solvent *in vacuo*, diol **4.24** was obtained in sufficient purity (157mg, 99%): R_f = 0.21 (80% EtOAc/Hexanes); IR (thin film) 3380, 2933, 2859, 1686, 1651 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.76-7.78 (m, 4H), 7.71-7.73 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.25-7.30 (m, 6H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.85 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.26 (m, 1H), 4.88 (d, *J* = 15.5 Hz, 1H), 4.34 (m, 1H), 4.14-4.18 (m, 2H), 3.92-4.01 (m, 7H), 3.73 (m, 1H), 3.69 (s, 3H), 3.44 (s, 3H), 3.41 (s, 1H), 3.24-3.30 (m, 2H), 2.65-2.69 (m, 1H), 2.46-2.51 (m, 1H), 2.27 (s, 3H), 1.94-1.99 (m, 2H), 1.90 (s, 3H), 1.13 (s, 9H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 153.47, 150.53, 149.59, 144.44, 137.26, 135.94, 135.90, 135.85, 135.10, 134.02, 133.84, 130.24, 130.11, 129.90, 129.66, 128.22, 128.02, 126.94, 119.52, 117.69, 114.76, 112.30, 111.66, 84.90, 69.38, 66.35, 65.16, 64.33, 55.91, 55.57, 53.37, 46.12, 44.31, 37.86, 36.87, 36.04, 31.05, 27.05, 21.68, 21.15, 20.01, 19.35, 19.03; MS (ESI) calcd for $C_{52}H_{61}N_3O_{10}S_2Si$ [M+Li] 986; found [M+li] 986.



Lactam 4.30: To a mixture of alcohol **4.23** (80 mg, 0.082 mmol) and imidazole (14 mg, 0.204 mmol) in anhydrous DMF (1.5 mL) at 20 °C was added TBSCl (14 mg, 0.090 mmol). The reaction mixture was stirred for 12 h at 20 °C, and then partitioned between water and EtOAc after 12 h reaction time. Organic layer was washed with brine and dried over Na_2SO_4. Column purification (silica gel, 60 → 70% EtOAc/Hexanes) after removal of solvents afforded lactam **4.30** (85 mg, 96%): R_f = 0.50 (80% EtOAc/Hexanes); IR (thin film) 2932, 2861, 1737, 1694 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.78 (d, *J* = 8.5 Hz, 2H), 7.69-7.72 (m, 4H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.20-7.24 (m, 6H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.76 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H), 6.60 (d, *J* = 8.0 Hz, 1H), 4.77 (d, *J* = 15.5 Hz, 1H), 4.32 (dd, *J* = 7.0, 3.0 Hz, 1H), 4.22-4.26 (m, 2H), 4.06-4.18 (m, 3H), 3.98 (d, *J* = 15.5 Hz, 1H), 3.92 (m, 1H), 3.67 (m, 1H), 3.56 (s, 3H), 3.39 (s, 3H), 3.10 (dd, *J* = 7.0, 3.0 Hz, 1H), 2.96 (m, 1H), 2.23 (m, 2H), 1.93 (m, 1H), 1.95 (s, 3H), 1.85 (s, 3H), 1.82 (m, 1H), 1.12 (s, 9H), 0.98 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 172.94, 153.80, 150.51, 149.56, 144.57, 144.10, 137.71, 136.04, 135.83, 133.84, 133.79, 130.28, 130.00, 129.97, 129.65, 129.39, 128.21, 128.05, 128.03, 127.86, 120.29, 119.44, 114.52, 112.16, 111.43, 65.05, 64.70, 64.31, 55.69, 55.44, 52.96, 44.26, 41.85,

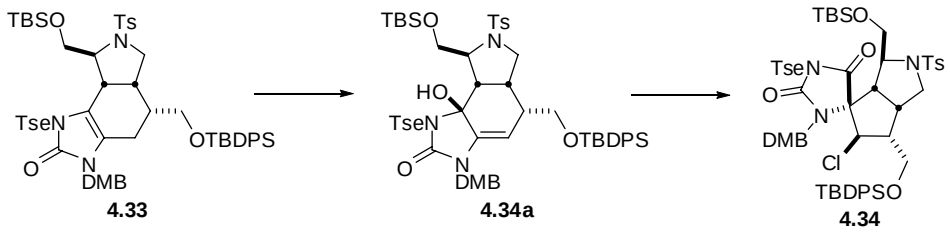
37.71, 36.29, 34.88, 27.03, 26.12, 21.18, 21.04, 20.04, 19.33, 18.51, -5.36, -5.43; HRMS (MALDI) calcd for $C_{58}H_{73}N_3O_{10}S_2Si_2$ [M+H] 1092.4354; found [M+H] 1092.4388.



Acetate 4.32: To a solution of lactam **4.30** (85 mg, 0.078 mmol) in CH_2Cl_2 (0.8 mL) at -78 °C was added DIBAl-H (0.10 mL DIBAl-H in 0.3 mL CH_2Cl_2, 0.56 mmol). The reaction was stirred at -78 °C for 3 h. Upon completion of the reaction, to the reaction mixture was added Rochelle's salt solution (5 mL) at -78 °C. The mixture was allowed to warm to 20 °C and stirred vigorously for 4 h. Then the mixture was transferred into a separation funnel and extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layer was washed with brine and dried further over Na_2SO_4. After removal of solvent *in vacuo*, aminal **4.31** was obtained in sufficient purity for next step (85mg, 100%).

To a solution of aminal **4.31** (80 mg, 0.073 mmol) in CH_2Cl_2 (1.0 mL) at 0 ºC was added pyridine (0.18 mL, 2.19 mmol), followed by acetic anhydride (0.14 mL, 1.46 mmol). The reaction mixture was warmed to 20 °C and stirred for 10 h. Then volatile compounds in the reaction mixture were removed *in vacuo*. Purification of the residue by column chromatography (silica gel, 60 → 70% EtOAc/ Hexanes) afforded the acetate **4.32** as a colorless foam (83 mg, 99%): R_f = 0.45 (80% EtOAc/Hexanes); IR (thin film) 2931, 2861, 1745, 1690 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.68-7.72 (m, 4H),

7.64-7.66 (m, 4H), 7.21-7.25 (m, 6H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.63-6.66 (m, 4H), 4.95 (d, *J* = 15.5 Hz, 1H), 4.31 (dd, *J* = 10.0, 4.0 Hz, 1H), 4.03-4.15 (m, 3H), 3.87 (m, 1H), 3.81 (m, 1H), 3.73 (d, *J* = 15.5 Hz, 1H), 3.67 (d, *J* = 8.0 Hz, 2H), 3.63 (s, 3H), 3.62 (m, 1H), 3.41 (s, 3H), 2.91-2.96(m, 2H), 2.36 (m, 1H), 2.13 (s, 3H), 1.98 (m, 1H), 1.83 (s, 3H), 1.80 (m, 1H), 1.75 (s, 3H), 1.11 (s, 9H), 1.06 (s, 9H), 0.27 (s, 6H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 169.74, 153.48, 150.62, 149.58, 144.11, 144.04, 137.87, 135.82, 135.68, 134.88, 133.71, 133.48, 130.36, 130.08, 130.04, 129.68, 129.66, 128.21, 128.05, 127.79, 127.06, 119.42, 117.65, 114.30, 112.18, 111.46, 82.42, 66.11, 65.63, 65.22, 55.77, 55.50, 52.60, 44.19, 44.14, 37.48, 36.92, 36.14, 26.90, 26.31, 21.50, 21.15, 21.02, 20.08, 19.30, 18.78, -5.22, -5.32; HRMS (MALDI) calcd for $C_{60}H_{77}N_3O_{11}S_2Si_2$ [M+H] 1136.4616; found [M+H] 1136.4585.

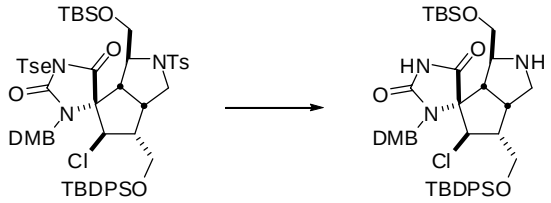


Chlorocyclopentane 4.34: To a mixture of pyrrolidine **4.33** (78 mg, 0.072 mmol) and $MgSO_4$ (~100 mg) in CH_2Cl_2 (4.8 mL) at -60 ºC was added freshly prepared DMDO (~0.07 M in acetone, 1.2 mL, 0.084 mmol). The reaction mixture was stirred for 2 h at -50 ºC. The reaction was quenched with 30 μL dimethylsulfide at -50 ºC after 2 h reaction time. The reaction mixture was then warmed to 20 °C and filtered to remove

$MgSO_4$. Intermediate **4.34a** was obtained in sufficient purity after removal of solvents *in vacuo* and was used directly for next step.

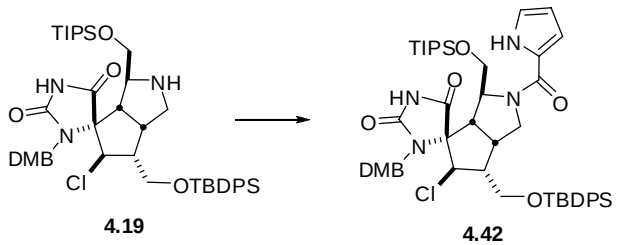
A mixture of allylic alcohol **4.34a** (79 mg, 0.072 mmol) and $MgSO_4$ (~100 mg) in CH_2Cl_2 (7.0 mL) was cooled to -60 ºC and cyclohexene (37 μL, 0.36 mmol) was added, followed by chloramine-T (33 mg, 0.145 mmol). The reaction mixture was allowed to warm to 20 °C slowly and stirred for 12 h. Then the reaction mixture was partitioned between water and methylene chloride. Organics were combined and dried over Na_2SO_4. Column purification (silica gel, 30 → 40% EtOAc/Hexanes) after removal of solvents afforded chlorocyclopentane **4.34** (49 mg, 60% over two steps): R_f = 0.76 (80% EtOAc/Hexanes); IR (thin film) 2959, 2858, 1771, 1716 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.85-7.88 (m, 4H), 7.68-7.73 (m, 4H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.22-7.28 (m, 6H), 6.82-6.85 (m, 4H), 6.50 (d, *J* = 8.0 Hz, 1H), 5.52 (d, *J* = 16.0 Hz, 1H), 4.91 (d, *J* = 16.0 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.52 (s, 1H), 4.24 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.93 (m, 1H), 3.82-3.86 (m, 1H), 3.71-3.79 (m, 3H), 3.70 (s, 3H), 3.62-3.68 (m, 2H), 3.44-3.53 (m, 3H), 3.32 (s, 3H), 3.27 (m, 1H), 3.04 (m, 1H), 1.92 (s, 3H), 1.86 (s, 3H), 1.16 (s, 9H), 0.79(s, 9H), 0.01 (s, 3H), -0.18 (s, 3H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 173.63, 156.89, 150.25, 149.61, 144.55, 142.95, 137.94, 136.21, 135.98, 135.95, 133.32, 133.06, 130.39, 130.06, 130.03, 129.80, 129.67, 129.38, 128.98, 128.21, 128.02, 127.82, 127.61, 127.03, 126.63, 120.81, 112.52, 112.04, 76.40, 65.02, 63.95, 62.89, 61.90, 59.94, 59.28, 55.68, 55.29, 54.31, 50.97, 50.07, 47.03, 45.48, 43.49, 33.32, 30.84, 27.04, 25.86, 25.62, 21.05, 20.96, 20.42, 19.30, 19.24, 18.05,

13.65, -5.73, -5.77; HRMS (ESI) calcd for $C_{58}H_{74}ClN_3O_{10}S_2Si_2$ [M+Na] 1150.3940, [M+K] 1166.3680; found [M+Na] 1150.4075, [M+K] 1166.3693.



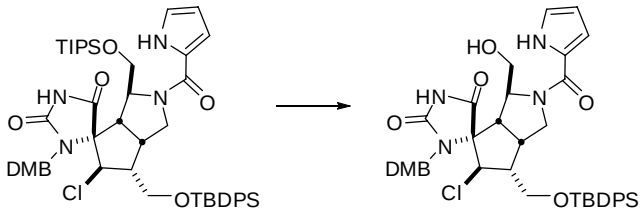
Pyrrolidine 4.35: To a solution of spirocycle **4.34** (33 mg, 0.029 mmol) in THF (0.6 mL) at -78 ºC was added 1.4 mL of freshly prepared sodium naphthalenide solution (0.105 M, 0.15 mmol) dropwise. The reaction was kept at -78 ºC for 5 min, and then quenched with pH 7 buffer (2 mL) at -78 ºC. After warming up to 20 °C, the reaction mixture was partitioned between water (5 mL) and EtOAc (3 X 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Column purification (silica gel, 40 → 50% EtOAc/Hexanes) after removal of solvents afforded pyrrolidine **4.35** (13 mg, 56%): R_f = 0.50 (70% EtOAc/Hexanes); IR (thin film) 3272, 2955, 2858, 1723 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.71-7.73 (m, 4H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.22-7.24 (m, 7H), 7.03 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 4.81 (d, *J* = 15.5 Hz, 1H), 4.77 (d, *J* = 15.5 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 3.92 (m, 1H), 3.72 (m, 1H), 3.59 (s, 3H), 3.39 (s, 3H), 3.29-3.38 (m, 3H), 3.22 (m, 1H), 3.03 (m, 1H), 2.96 (m, 1H), 2.88 (t, *J* = 10.5 Hz, 1H), 2.82 (m, 1H), 2.60 (dd, *J* = 8.0, 2.0 Hz, 1H), 1.15 (s, 9H), 0.90 (s, 9H), -

0.03 (s, 6H); HRMS (ESI) calcd for $C_{42}H_{58}ClN_3O_6Si_2$ [M+H] 792.3631; found [M+H] 792.3633.



Pyrrole 4.42: To a solution of pyrrolidine **4.19** (45 mg, 0.054 mmol) and pyrrole-2-carbonyl chloride[61] (35 mg, 0.27 mmol) in anhydrous methylene chloride (1.5 mL) was added triethylamine (12 μL, 0.085 mmol) at 20 °C. After being stirred for 20 min at 20 °C, the reaction mixture was partitioned between water (10 mL) and EtOAc (3 X10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of solvents *in vacuo*, column purification (silica gel, 30 → 40% EtOAc/Hexanes) afforded pyrrole **4.42** as a pale-yellow foam (37 mg, 74%): R_f = 0.18 (40% EtOAc/Hexanes); IR (thin film) 3268, 2948, 2865, 1773, 1725 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 10.95 (s, 1H), 10.20 (s, 1H), 7.58-7.64 (m, 4H), 7.20-7.28 (m, 6H), 6.93-6.95 (m, 2H), 6.77 (s, 1H), 6.69 (s, 1H), 6.46 (d, *J* = 2.5 Hz, 1H), 6.16 (s, 1H), 5.40 (d, *J* = 16.5 Hz, 1H), 4.94 (s, 1H), 4.21-4.31 (m, 3H), 4.04 (t, *J* = 9.5 Hz, 1H), 3.88 (m, 1H), 3.79 (d, *J* = 8.5 Hz, 1H), 3.50-3.55 (m, 4H), 3.45 (s, 3H), 3.37 (s, 3H), 3.30-3.34 (m, 1H), 1.02-1.11 (m, 30 H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 174.60, 160.50, 158.14, 150.02, 149.43, 135.92, 135.80, 133.03, 132.99, 130.11, 130.08, 129.92, 128.20, 128.02,

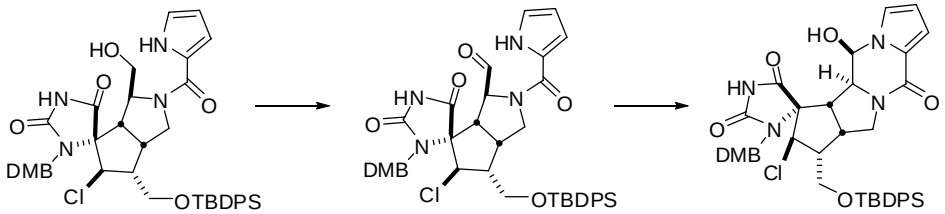
127.82, 125.46, 122.84, 120.15, 114.25, 111.88, 111.20, 110.48, 77.23, 64.16, 61.97, 61.47, 59.03, 55.18, 55.08, 50.54, 49.73, 46.67, 44.54, 43.74, 26.94, 19.24, 19.16, 18.09, 12.07; HRMS (ESI) calcd for $C_{50}H_{67}ClN_4O_7Si_2$ [M+Li] 933.4397; found [M+Li] 933.4373.



4.42 **4.43**

Alcohol 4.43: To a solution of pyrrole **4.42** (60 mg, 0.065 mmol) in methanol (3.2 mL) was added *p*-toluenesulofonic acid (*p*TSA, 18 mg, 0.097 mmol). The reaction was stirred at 20 °C for 16 h. PH 7 buffer (10 mL) was added to the reaction after 16 h. The resulting mixture was partitioned between water (20 mL) and EtOAc (3 X20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of solvents *in vacuo*, column purification (silica gel, 80 → 100% EtOAc/Hexanes) afforded monodeprotected alcohol **4.43** (35 mg, 70%): R_f = 0.12 (80% EtOAc/Hexanes); IR (thin film) 3275, 2934, 2857, 1770, 1723 cm^{-1}; ^{1}H-NMR (500 MHz, acetone-d_6) δ = 10.97 (s, 1H), 10.11 (s, 1H), 7.61-7.68 (m, 4H), 7.40-7.50 (m, 6H), 7.10 (s, 1H), 6.55-6.65 (m, 4H), 6.24 (m, 1H), 5.06 (d, *J* = 15.5 Hz, 1H), 4.67 (t, *J* = 4.5 Hz, 1H), 4.25 (d, *J* = 11.5 Hz, 2H), 4.16 (s, 2H), 3.93 (dd, *J* = 3.5, 11.0 Hz, 1H), 3.88 (d, *J* = 16.0 Hz, 1H), 3.66-3.75 (m, 4H), 3.63 (s, 3H), 3.46 (s, 3H), 3.33 (bs, 1H), 3.05 (bs, 1H), 0.97-1.03 (s, 9 H);

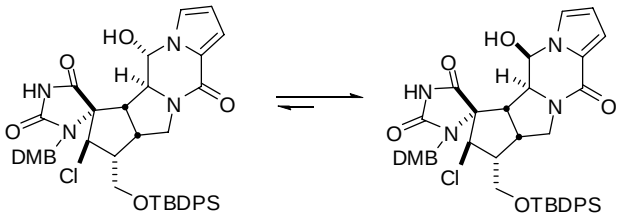
^{13}C-NMR (125 MHz, acetone-d_6) δ = 174.48, 160.13, 156.92, 149.49, 149.00, 135.81, 135.71, 133.00, 130.21, 130.17, 128.14, 128.10, 125.85, 122.35, 120.01, 113.60, 111.70, 111.20, 109.97, 76.77, 62.94, 61.81, 61.65, 59.65, 55.24, 54.93, 50.63, 48.97, 46.91, 43.87, 43.58, 26.63, 19.05; HRMS (MALDI) calcd for $C_{41}H_{47}ClN_4O_7Si$ [M+H] 771.2975; found [M+H] 771.2967.



***N,O*-Acetal 4.46**: To a reaction vial containing alcohol **4.43** (24 mg, 0.031 mmol) was added a solution of IBX in DMSO (17 mg IBX in 2.0 mL DMSO, 0.062 mmol). The reaction mixture was stirred for 21 h at 20 °C. After 21 h, the reaction mixture was partitioned between water (10 mL) and EtOAc (3 X10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of solvents *in vacuo*, the crude product was run through a silica gel plug to remove the baseline material to afford the aldehyde **4.45** (24 mg, 99%).

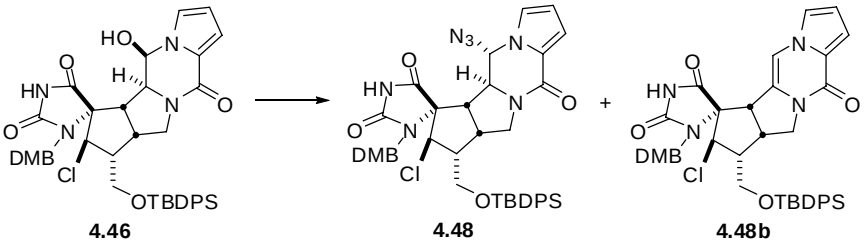
Aldehyde **4.45** (4.0 mg, 0.0052 mmol) was dissolved in anhydrous DMSO (0.50 mL) and the resulting solution was heated to 70 °C and stirred for 18 h. After the reaction time, the reaction mixture was partitioned between water (10 mL) and EtOAc (3 X10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4.

After removal of solvents *in vacuo*, column purification (silica gel, 20 → 30% acetone/CH_2Cl_2) afforded *N,O*-acetal **4.46** (2.8 mg, 70%): R_f = 0.68 (50% acetone/CH_2Cl_2); IR (thin film) 3275, 2934, 2857, 1770, 1723 cm^{-1}; ^{1}H-NMR (500 MHz, acetone-d_6) δ = 7.67-7.70 (m, 4H), 7.42-7.50 (m, 6H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.73 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.63 (s, 1H), 6.62 (s, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 6.08 (t, *J* = 3.5 Hz, 1H), 5.81 (d, *J* = 7.5 Hz, 1H), 5.23 (d, *J* = 5.5 Hz, 1H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.56 (s, 2H), 4.12-4.16 (m, 2H), 4.02 (dd, *J* = 3.5, 11.0 Hz, 1H), 3.81-3.84 (m, 1H), 3.68 (s, 3H), 3.64 (s, 3H), 3.62-3.66 (m, 1H), 3.51 (dd, *J* = 5.5, 9.0 Hz, 1H), 3.36-3.40 (m, 1H), 3.08-3.12 (m, 1H), 1.09 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6) δ = 174.24, 158.11, 157.16, 149.71, 149.22, 135.76, 135.73, 133.39, 132.88, 130.42, 130.23, 130.19, 128.17, 128.11, 124.03, 122.86, 120.11, 112.26, 111.88, 111.53, 109.42, 77.11, 76.49, 61.74, 61.66, 58.43, 55.37, 55.11, 19.94, 46.11, 45.60, 44.70, 41.69, 26.71, 19.15; HRMS (MALDI) calcd for $C_{41}H_{45}ClN_4O_7Si$ [M+H] 769.2819; found [M+H] 769.2789.



***N,O*-Acetal 4.46**: *N,O*-Acetal **4.47** (6.0 mg, 0.0078 mmol) was dissolved in anhydrous DMSO (0.80 mL) and the resulting solution was heated to 70 °C and stirred for 16 h. After the reaction time, the reaction mixture was partitioned between water (10 mL) and

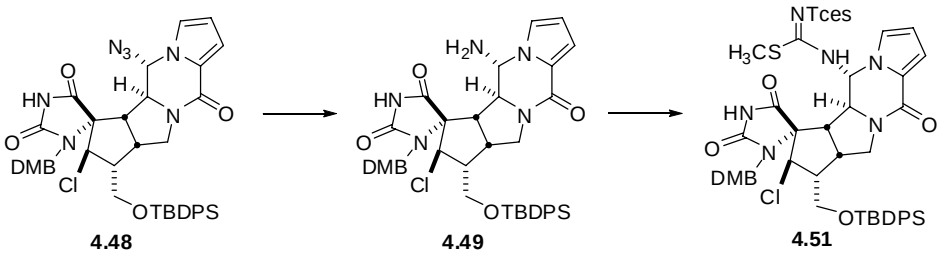
EtOAc (3 X10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of solvents *in vacuo*, column purification (silica gel, 10 → 20% acetone/CH_2Cl_2) afforded the epimerized *N*,*O*-acetal **4.46** (4.0 mg, 67%).



Azide 4.48 and pyrrolo-pyrazinone 4.48b: To a solution of alcohol **4.46** (6.0 mg, 0.0078 mmol) in anhydrous THF (0.80 mL) was added DPPA (4 μL, 0.012 mmol) at 0 °C, followed by DBU (3 μL, 0.020 mmol). The reaction was allowed to warm to 20 °C and stirred for 29 h. The reaction mixture was then partitioned between water (10 mL) and EtOAc (2 X 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of solvents *in vacuo*, column purification (silica gel, 40 → 60% EtOAc/Hexanes) afforded two products: azide **4.48** (4.0 mg, 67%) and pyrrolo-pyrazinone **4.48b** (1.5 mg, 25%). Azide **4.48**: R_f = 0.76 (80% EtOAc/Hexanes); IR (thin film) 2928, 2854, 2117, 1729, 1637 cm^{-1}; ^{1}H-NMR (500 MHz, acetone-d_6) δ = 10.30 (bs, 1H), 7.68-7.70 (m, 4H), 7.44-7.50 (m, 6H), 7.05 (s, 1H), 7.03 (s, 1H), 6.81 (d, *J* = 6.5 Hz, 1H), 6.72 (d, *J* = 3.5 Hz, 1H), 6.51 (d, *J* = 8.5 Hz, 1H), 6.23 (t, *J* = 3.0 Hz, 1H), 5.58 (d, *J* = 10.0 Hz, 1H), 4.86 (d, *J* = 12.5 Hz, 1H), 4.65 (s, 2H), 4.20-4.24 (dd, *J* = 8.0, 12.0 Hz, 1H), 4.02-4.05 (dd, *J* = 4.0, 11.5 Hz, 1H), 3.82-3.86 (dd, *J* = 7.0, 11.0 Hz, 1H), 3.75-3.79

(m, 1H), 3.68 (s, 3H), 3.61 (s, 3H), 3.51-3.58 (m, 2H), 3.34-3.41 (m, 1H), 3.04-3.09 (m, 1H), 1.09 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6) δ = 174.44, 157.52, 156.21, 149.78, 149.36, 135.79, 135.75, 135.74, 133.22, 132.90, 130.26, 130.24, 129.93, 128.17, 128.12, 128.09, 125.02, 120.81, 120.51, 113.54, 112.20, 111.43, 110.44, 77.27, 73.63, 61.80, 61.63, 58.29, 55.31, 55.11, 51.87, 46.28, 46.04, 45.01, 42.49, 26.68, 19.14. MS (ESI) calcd for $C_{41}H_{44}ClN_7O_6Si$ [M+H] 794, found [M+H] 794.

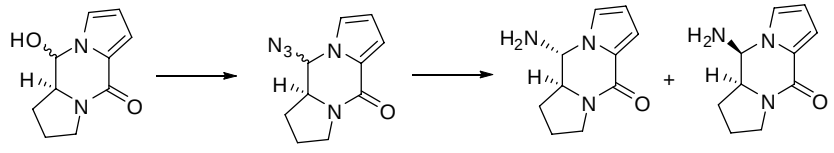
Pyrrolo-pyrazinone **4.48b**: R_f = 0.62 (80% EtOAc/Hexanes); IR (thin film) 2919, 2851, 1773, 1729 cm^{-1}; ^{1}H-NMR (500 MHz, acetone-d_6) δ = 10.1 (bs, 1H), 7.65-7.68 (m, 4H), 7.42-7.50 (m, 7H), 7.27 (dd, *J* = 1.5, 2.5 Hz, 1H), 6.93 (m, 1H), 6.85 (d, *J* = 2.5 Hz, 1H), 6.50-6.53 (m, 2H), 6.40 (d, *J* = 8.5 Hz, 1H), 4.63-4.66 (d, *J* = 16.0 Hz, 1H), 4.54-4.57 (d, *J* = 12.5 Hz, 1H), 4.41-4.45 (dd, *J* = 10.0, 13.0 Hz, 1H), 4.21-4.25 (m, 1H), 4.03-4.06 (dd, *J* = 3.0, 11.0 Hz, 1H), 3.81-3.84 (dd, *J* = 6.5, 11.0 Hz, 1H), 3.70 (s, 3H), 3.61 (dd, *J* = 3.0, 6.5 Hz, 1H), 3.57 (s, 3H), 3.45-3.48 (d, *J* = 16.0 Hz, 1H), 3.06-3.12 (m, 1H), 1.09 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6) δ = 173.68, 156.77, 154.25, 149.54, 149.08, 135.80, 135.79, 135.76, 133.28, 132.80, 130.24, 130.18, 129.83, 128.16, 128.09, 127.34, 124.26, 119.61, 119.47, 112.25, 111.52, 111.33, 108.87, 106.31, 77.31, 61.39, 59.25, 55.23, 55.07, 50.63, 47.72, 46.02, 44.48, 41.04, 29.94, 26.70, 19.12; HRMS (ESI) calcd for $C_{41}H_{43}ClN_4O_6Si$ [M+Li] 757.2800; found [M+Li] 757.2851.



Isothiourea 4.51: To a solution of azide **4.48** (2.0 mg, 0.0025 mmol) in anhydrous THF (0.20 mL) was added samarium diiodide (0.1 M solution in THF, 0.2 mL, 0.02 mmol) at -78 °C. The reaction was warmed to 20 °C and stirred for 10 min. Then the reaction was quenched with sat'd $NaHCO_3$. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, and dried over Na_2SO_4. After removal of solvents *in vacuo*, column purification (silica gel, 60 → 80% EtOAc/Hexanes) afforded the amine **4.49** (2 mg, 99%): R_f = 0.35 (80% EtOAc/Hexanes); ^{1}H-NMR (500 MHz, benzene-d_6) δ = 10.2 (bs, 1H), 7.68-7.71 (m, 4H), 7.44-7.52 (m, 6H), 7.07-7.10 (m, 2H), 6.84 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.69 (m, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.14 (t, *J* = 3.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.76 (d, *J* = 16.5 Hz, 1H), 4.66-4.72 (dd, *J* = 9.5, 19.5 Hz, 1H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.29-4.33 (dd, *J* = 8.0, 12.0 Hz, 1H), 4.01-4.04 (m, 1H), 3.80-3.84 (dd, *J* = 7.0, 10.5 Hz, 1H), 3.75-3.78 (m, 2H), 3.71 (s, 3H), 3.62 (s, 3H), 3.53-3.58 (t, *J* = 12.0 Hz, 1H), 3.47-3.50 (dd, *J* = 4.0, 9.0 Hz, 1H), 3.26-3.33 (m, 1H), 3.02-3.08 (m, 1H), 2.58-2.62 (m, 2H), 1.10 (s, 9H); HRMS (ESI) calcd for $C_{41}H_{46}ClN_5O_6Si$ [M+H] 768.2984; found [M+H] 768.2980.

To a solution of amine **4.49** (4.4 mg, 0.0057 mmol) in CH_2Cl_2 (0.60 mL) at 21 °C was added imidochloride (TcesN=C(SMe)Cl) (4.0 mg, 0.0114 mmol), followed by

Et_3N (3 μL, 0.0228 mmol). After 11 h at 21 °C, the reaction mixture was partitioned between water and EtOAc. The organic layer was washed with water and brine, and dried over Na_2SO_4. After removal of solvents *in vacuo*, column purification (silica gel, 50 % EtOAc/Hexanes) afforded the isothiourea **4.51** (4.6 mg, 77%): R_f = 0.60 (70% EtOAc/Hexanes); IR (thin film) 3420, 2931, 2857, 1741, 1700 cm^{-1}; ^{1}H-NMR (500 MHz, acetone-d_6) δ = 7.65-7.67 (m, 4H), 7.42-7.52 (m, 6H), 7.10 (s, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.77 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.68 (dd, *J* = 1.5, 3.5 Hz, 1H), 6.44 (d, *J* = 8.0 Hz, 1H), 6.12 (t, *J* = 3.0 Hz, 1H), 5.04 (s, 2H), 4.91-4.98 (d, *J* = 16.0 Hz, 1H), 4.85 (d, *J* = 12.0 Hz, 1H), 4.71-4.77 (dd, *J* = 9.5, 19.0 Hz, 1H), 4.52 (d, *J* = 16.0 Hz, 1H), 4.30-4.34 (dd, *J* = 8.5, 12.5 Hz, 1H), 4.01-4.04 (dd, *J* = 3.0, 10.5 Hz, 1H), 3.79-3.85 (m, 2H), 3.74 (s, 3H), 3.57-3.62 (m, 2H), 3.59 (s, 3H), 3.33-3.40 (m, 1H), 2.92-2.98 (m, 1H), 2.79 (s, 3H), 2.44-2.54 (bs, 1H), 1.08 (s, 9H); ^{13}C-NMR (125 MHz, acetone-d_6) δ = 169.68, 156.94, 149.97, 149.40, 135.76, 133.27, 132.80, 130.26, 130.22, 129.12, 128.17, 128.09, 125.02, 120.30, 119.93, 113.00, 111.54, 111.36, 108.87, 79.70, 68.56, 61.32, 59.01, 55.39, 55.15, 46.75, 46.26, 45.94, 42.29, 36.57, 29.94, 26.69, 19.13, 16.42; HRMS (ESI) calcd for $C_{45}H_{50}Cl_4N_6O_9S_2Si$ [M+H] 1051.1682; found [M+H] 1051.1678.

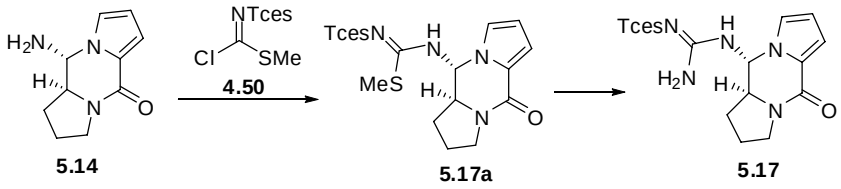


5.9 **5.13** **5.14** **5.15**

***N,N*-hemiacetal 5.14 and 5.15**: To a stirred solution of *N,O*-acetal **5.9** (325 mg, 1.69 mmol) in THF (17 mL) was added DPPA (0.40 mL, 1.86 mmol) dropwise at 0 °C, followed by the dropwise addition of DBU (0.28 mL, 1.86 mmol). The reaction was stirred at 21 °C for 10 h. The reaction mixture was then partitioned between water and EtOAc. Following extraction with EtOAc (3 X 50mL), the combined organic layers were washed with H_2O, brine, and then dried over anhydrous Na_2SO_4. Solvents were removed *in vacuo* and the residue was purified by flash chromatography (silica gel, 60 → 80% EtOAc/hexanes) to furnish the azide product as a ~1:1 mixture of diastereomers (230 mg, 63%).

A portion of azides **5.13** produced above (inseparable mixture of diastereomers, dr ~3:4) (56 mg, 0.26 mmol) were dissolved in anhydrous MeOH, the solution was charged with Pd/C (~ 10 mg), and then purged with hydrogen gas. The reaction mixture was stirred under H_2 atmosphere at 21 °C for 18 h. The reaction mixture was filtered through Celite® and concentrated to give aminals **5.14** and **5.15** which were separated by flash column chromatography (silica gel, EtOAc to 5% MeOH/EtOAc) to give aminal **5.14** (15 mg, 31%) and the diastereomeric aminal **5.15** (20 mg, 39%). Aminal **5.14**: R_f = 0.26 (10% MeOH/EtOAc); $[\alpha]_D$: +91.2 (0.90, $CHCl_3$); IR (thin film) 3381, 2975, 2881, 1629 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.04 (dd, *J* = 2.0, 2.5 Hz, 1H), 6.87 (dd, *J* = 2.0, 4.0 Hz, 1H), 6.21 (dd, *J* = 2.5, 4.0 Hz, 1H), 4.61 (d, *J* = 10.0 Hz, 1H), 3.68 (m, 1H), 3.50-3.61 (m, 2H), 2.45 (bs, 2H), 2.34 (m, 1H), 2.02-2.06 (m, 1H), 1.80-1.87 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 158.26, 125.46, 119.47, 113.70, 110.13, 69.21, 64.11, 45.02, 30.79, 23.14; HRMS (ESI) Calcd for $C_{10}H_{13}N_3O$ [M+H]: 192.1137, found:

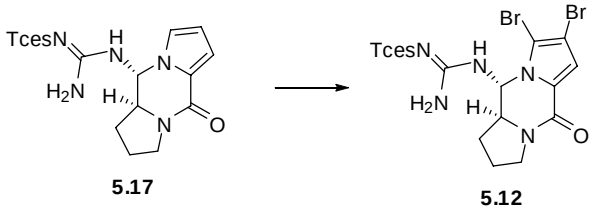
192.1141. Aminal **5.15**: R_f= 0.15 (10% MeOH/EtOAc); IR (thin film) 3378, 2973, 2878, 1629 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 1.5, 3.5 Hz, 1H), 6.86 (dd, *J* = 2.0, 2.5 Hz, 1H), 6.22 (dd, *J* = 2.5, 3.5 Hz, 1H), 5.02 (d, *J* = 3.0 Hz, 1H), 4.13 (m, 1H), 3.78 (m, 1H), 3.56 (m, 1H), 2.09-2.26 (m, 5H), 1.89-1.95 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 158.36, 123.77, 121.74, 113.48, 110.76, 65.13, 61.17, 44.57, 28.19, 23.61; HRMS (ESI) Calcd for $C_{10}H_{13}N_3O$ [M+H]: 192.1137, found: 192.1141.



Tces-protected guanidine 5.17: To a stirred solution of aminal **5.14** (0.843 g, 4.40 mmol) and imidochloride **4.50** (2.12 g, 6.60 mmol) in CH_2Cl_2 (30.0 mL) was added triethylamine (1.86 mL, 13.2 mmol) dropwise at 21 °C. The reaction mixture was stirred for 16 h and then concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 80% EtOAc/hexanes to EtOAc to give the isothiourea intermediate **5.17a** (1.95 g, 93%).

The isothiourea **5.17a** (1.9 g, 4.0 mmol) was dissolved in CH_3CN and the reaction mixture was charged with HMDS (2.1 mL, 10 mmol) and $HgCl_2$ (1.2 g, 4.4 mmol) sequentially. After being stirred for 18 h at 21 °C, the reaction mixture was filtered to remove solid residue. The filtrate was concentrated in *vacuo* and purified by flash chromatography (silica gel, 80% EtOAc/hexanes to EtOAc) to give Tces-protected

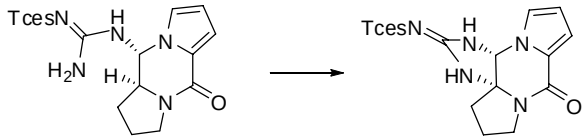
guanidine **5.17** as a white solid (1.4 g, 77%). The product was recrystallized in MeOH to give slightly pink thin needle crystals. After slow evaporation of an EtOH solution of the compound, a colorless needle crystal was obtained and was suitable for X-ray crystallography. The crystal structure of **5.17** confirmed its identity (crystallographic data submitted to the Cambridge Crystallographic Data Centre, reference number: CCDC-652212). R_f = 0.12 (EtOAc); $[\alpha]_D$: -49.1 (0.91, CH_3CN); IR (thin film) 3440, 3323, 2952, 1628 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3CN) δ 7.25 (d, *J* = 9.5 Hz, 1H), 6.92 (bs, 2H), 6.85 (t, *J* = 2.0 Hz, 1H), 6.69 (dd, *J* = 1.5, 3.5 Hz, 1H), 6.17 (dd, *J* = 2.5, 3.5 Hz, 1H), 5.88 (bs, 1H), 4.62 (s, 2H), 3.89 (m, 1H), 3.54 (m, 1H), 3.42 (m, 1H), 2.20 (m, 1H), 2.02 (m, 1H), 1.80-1.85 (m, 2H); ^{13}C-NMR (125 MHz, CD_3CN) δ 157.90, 157.79, 125.02, 121.07, 113.39, 110.22, 94.42, 78.15, 66.17, 61.05, 44.96, 29.55, 22.83; HRMS (ESI) Calcd for $C_{13}H_{16}Cl_3N_5O_4S$ [M+Li]: 450.0149, found: 450.0143.



5.17 **5.12**

Tces-protected guanidine 5.12: To a slurry of guanidine **5.17** (5.0 mg, 0.011 mmol) in CH_2Cl_2 (0.30 mL) was added NBS (4.0 mg, 0.023 mmol). The reaction was stirred for 2 h at 21 °C and then concentrated *in vacuo*. Column purification of the crude product (silica gel, 50 → 90 % EtOAc/Hexanes) afforded the Tces-guanidine **5.12** (6.7 mg, 99%): R_f = 0.21 (EtOAc); $[\alpha]_D$: -13.8 (*c* 0.33, 1:2 MeOH:CH_2Cl_2); IR (thin film) 3443, 3368,

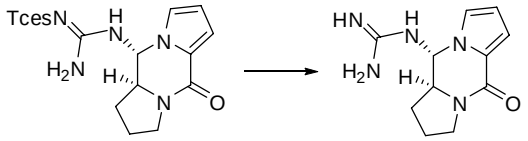
1642 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3CN) δ 6.89 (s, 1H), 6.60-6.76 (bs, 2H), 6.56 (d, *J* = 10.0 Hz, 1H), 6.18-6.23 (t, *J* = 10.0 Hz, 1H), 4.64 (s, 2H), 3.95-4.06 (m, 1H), 3.61-3.65 (m, 1H), 3.44-3.50 (m, 1H), 2.23-2.26 (m, 1H), 2.03-2.08 (m, 1H), 1.84-1.90 (m, 2H); ^{13}C-NMR (125 MHz, CD_3CN) δ 157.25, 155.54, 128.88, 118.22, 115.23, 104.12, 102.62, 78.19, 68.39, 61.04, 44.98, 29.59, 22.44; HRMS (ESI) Calcd for $C_{13}H_{14}Br_2Cl_3N_5O_4S$ [M+H]: 599.8277, found: 599.8248.



Tces-protected phakellin 5.18: To a mixture of guanidine **5.17** (8.0 mg, 0.018 mmol), $PhI(OAc)_2$ (23 mg, 0.072 mmol) and MgO (2.0 mg, 0.036 mmol) in a microwave reaction tube was added 1.0 mL of CH_3CN. The reaction tube was placed in a microwave reactor and heated (150 Watts) for 10 min. The reaction mixture was concentrated in *vacuo* and subjected to column chromatography (silica gel , 60 → 80% EtOAc/hexanes) to yield the cyclized product **5.18** (3.0 mg, 38%): R_f = 0.35 (EtOAc); $[\alpha]_D$: +40.4 (0.70, CH_2Cl_2); IR (thin film) 3362, 2923, 2851, 1611 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3CN) δ 7.86 (s, 1H), 7.42 (s, 1H), 7.03 (dd, *J* = 1.5, 2.5 Hz, 1H), 6.76 (dd, *J* = 1.5, 4.0 Hz, 1H), 6.33 (dd, *J* = 2.5, 4..0 Hz, 1H), 5.80 (s, 1H), 4.54 (s, 2H), 3.72-3.76 (m, 1H), 3.51-3.57 (m, 1H), 2.29-2.34 (m, 2H), 2.07-2.12 (m, 2H); ^{13}C-NMR (125 MHz, CD_3CN) δ 157.63, 156.04, 123.94, 122.24, 112.59, 112.08, 94.20, 81.97, 78.07, 68.16,

45.16, 38.92, 19.88; HRMS (ESI) Calcd for $C_{13}H_{14}Cl_3N_5O_4S$ [M+Li]: 447.9992, found: 447.9972.

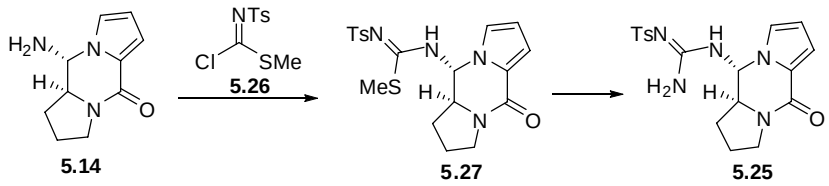
Note: On ~10 mg scale, the reaction reproducibly gave 30-38% yield; in one instance, scaling up to 83 mg led to a decrease of yield (22%).



5.17 **5.23**

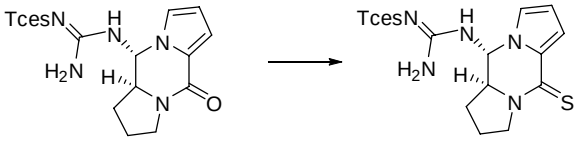
Guanidine 5.23: To a mixture of Tces-protected guanidine **5.17** (91 mg, 0.205 mmol) and zinc powder (67 mg, 1.025 mmol) in MeOH (3.0 mL) was added acetic acid (35 μL, 0.615 mmol). The reaction mixture was heated to 50 °C and stirred vigorously for 3 h. After cooling to 20 °C, the reaction mixture was filtered through Celite® to remove zinc residues. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography (silica gel, 5 → 30 % MeOH/CH_2Cl_2) to give the guanidine **5.23** (35 mg, 75%): R_f = 0.09 (20% CH_3OH/CH_2Cl_2); $[\alpha]_D$: -26.6 (*c* 1.60, CH_3OH); IR (thin film) 3429, 3331, 2979, 1623 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD) δ 7.01 (dd, *J* = 1.5, 2.5 Hz, 1H), 6.83 (dd, *J* = 1.5, 4.0 Hz, 1H), 6.20 (dd, *J* = 2.5, 4.0 Hz, 1H), 5.85 (d, *J* = 10.5 Hz, 1H), 3.92-3.97 (m, 1H), 3.69-3.74 (m, 1H), 3.55-3.60 (m, 1H), 2.30-2.34 (m, 1H), 2.10-2.14 (m, 1H), 1.92-1.98 (m, 2H); ^{13}C-NMR (125 MHz, CD_3OD) δ 160.12,

156.86, 125.02, 122.92, 114.83, 110.80, 67.05, 62.59, 46.02, 30.49, 23.84; MS (ESI) calcd for $C_{11}H_{15}N_5O$ [M+H]: 234, found: [M+H]: 234.



Tosyl-guanidine 5.25: To a stirred solution of aminal **5.14** (23.0 mg, 0.120 mmol) and imidochloride **5.26** (TsN=C(SMe)Cl) (38 mg, 0.144 mmol) in anhydrous CH_3CN (1.2 mL) was added Hünig's base (diisopropylethylamine, 105 μL, 0.600 mmol) dropwise at 21 °C. The reaction mixture was heated to 45 °C and stirred for 24 h. After removal of solvents *in vacuo*, the crude product was purified by flash chromatography on silica gel eluting with 80% EtOAc/hexanes to EtOAc to give the isothiourea intermediate **5.27** (15 mg, 30%): R_f = 0.17 (EtOAc); $[\alpha]_D$: +17.4 (*c* 1.20, CH_2Cl_2); IR (thin film) 3248, 2925, 1629 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.77 (d, *J* = 10.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.97(m, 1H), 6.72 (m, 1H), 6.26 (m, 1H), 5.57-5.61 (t, *J* = 10.0 Hz, 1H), 3.92-3.97 (m, 1H), 3.79-3.83 (m, 1H), 3.57-3.63 (m, 1H), 2.45 (s, 3H), 2.44 (s, 3H), 2.29-2.34 (m, 1H), 2.11-2.17 (m, 1H), 1.85-1.98 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 168.77, 157.50, 143.91, 138.62, 129.80, 126.59, 125.19, 120.08, 114.86, 111.23, 69.19, 61.95, 44.88, 29.91, 22.97, 21.75, 14.73; MS (ESI) calcd for $C_{19}H_{22}N_4O_3S_2$ [M+H]: 419, found: [M+H]: 419.

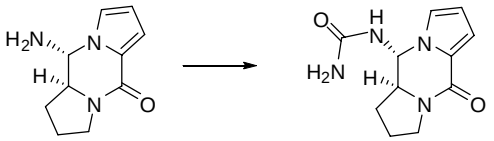
The isothiourea **5.27** (10 mg, 0.024 mmol) was dissolved in CH_3CN (1.0 mL) and the solution was charged with HMDS (12 μL, 0.060 mmol) and $HgCl_2$ (13 mg, 0.048 mmol) sequentially. After being stirred for 3 h at 21 °C, the reaction mixture was filtered to remove solid residue. The filtrate was concentrated in *vacuo* and purified by flash chromatography (silica gel, EtOAc to 5% MeOH/EtOAc) to give tosyl-protected guanidine **5.25** as a white solid (10 mg, 99%): R_f = 0.09 (EtOAc); $[\alpha]_D$: -19.8 (*c* 0.92, CH_3CN); IR (thin film) 3435, 3331, 2922, 1623 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3CN) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.68 (dd, *J* = 1.5, 3.5 Hz, 1H), 6.60 (dd, *J* = 1.5, 2.5 Hz, 1H), 6.48 (bs, 1H), 6.11 (dd, *J* = 2.5, 3.5 Hz, 1H), 5.80 (m, 1H), 3.82-3.87 (m, 1H), 3.56-3.61 (m, 1H), 3.41-3.47 (m, 1H), 2.40 (s, 3H), 2.05-2.09 (m, 1H), 1.97-2.02 (m, 1H), 1.80-1.85 (m, 1H), 1.66-1.72 (m, 1H); ^{13}C-NMR (125 MHz, CD_3CN) δ 158.03, 157.62, 143.62, 141.61, 130.26, 126.82, 126.13, 121.13, 113.51, 110.48, 66.93, 61.49, 45.44, 30.14, 23.47, 21.43; MS (ESI) calcd for $C_{18}H_{21}N_5O_3S$ [M+H]: 388, found: [M+H]: 388.



5.17 **5.29**

Tces-guanidine 5.29: To a solution of guanidine **5.17** (105 mg, 0.236 mmol) in anhydrous THF (5.0 mL) was added Belleau's reagent (124 mg, 0.236 mmol). The reaction mixture was heated to 60 °C. After 16 h, the reaction was quenched with sat'd

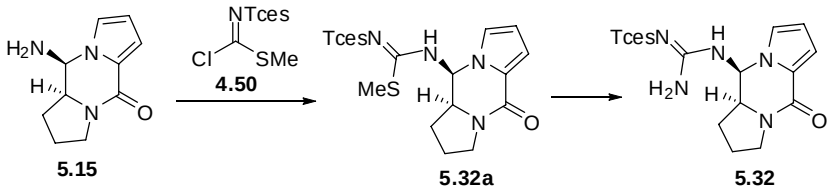
$NaHCO_3$ solution (5 mL) and the resulting mixture was partitioned between water (15 mL) and EtOAc (2 X 20 mL). The combined organics were washed with brine and dried further over Na_2SO_4. After removal of solvents *in vacuo*, the residue was purified by column chromatography (silica gel, 60 % EtOAc/Hexanes to EtOAc) to yield the piperazine-thione **5.29** (45 mg, 42%): R_f = 0.73 (EtOAc); $[\alpha]_D$: -9.4 (*c* 0.20, 1:1 CH_3OH:CH_2Cl_2); IR (thin film) 3458, 3343, 2946, 1626 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3CN) δ 7.01 (dd, *J* = 1.5, 4.0 Hz, 1H), 6.90 (dd, *J* = 2.0, 2.5 Hz, 1H), 6.60-6.80 (bs, 3H), 6.19 (dd, *J* = 2.5, 4.0 Hz, 1H), 5.98 (bs, 1H), 4.62 (s, 2H), 4.05-4.10 (m, 1H), 3.90-3.98 (m, 1H), 3.72-3.78 (m, 1H), 2.30-2.35 (m, 1H), 2.09-2.15 (m, 1H), 1.91-1.97 (m, 2H); ^{13}C-NMR (125 MHz, CD_3CN) δ 178.94, 157.49, 131.11, 120.96, 117.75, 110.84, 94.33, 78.17, 65.66, 62.60, 51.62, 29.66, 22.25; HRMS (ESI) Calcd for $C_{13}H_{16}Cl_3N_5O_3S_2$ [M+H]: 459.9838, found: [M+H]: 459.9859.



5.14 **5.31**

Urea 5.31: To a solution of amine **5.14** (40 mg, 0.21 mmol) in anhydrous THF (2.0 mL) was added trichloroacetyl isocyanate (62 μL, 0.52 mmol) at 20 °C. The reaction mixture was stirred for 10 min at 20 °C, then MeOH (3.0 mL) was added, followed by some silica gel (~ 1 g). The resulting slurry was heated to 45 °C and stirred vigorously for 24 h. The reaction mixture was then filtered (to remove silica gel) and the filtrate was

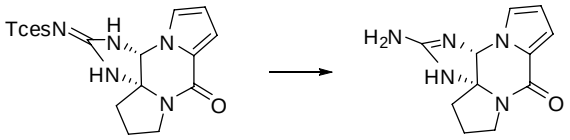
concentrated *in vacuo*. Due to the limited solubility of urea **5.31** in EtOAc, the crude product was washed with a small amount of EtOAc (~ 2 mL) to remove any impurities, affording urea **5.31** as a white solid (40 mg, 82%): R_f = 0.06 (EtOAc); $[\alpha]_D$: -19.6 (*c* 0.13, CH_3OH); IR (thin film) 3266, 3206, 1658, 1596 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD) δ 6.89 (dd, *J* = 1.5, 2.5 Hz, 1H), 6.84 (dd, *J* = 1.5, 4.0 Hz, 1H), 6.23 (dd, *J* = 2.5, 4.0 Hz, 1H), 5.67 (d, *J* = 10.5 Hz, 1H), 3.89-3.94 (m, 1H), 3.71-3.75 (m, 1H), 3.56-3.62 (m, 1H), 2.27-2.32 (m, 1H), 2.12-2.16 (m, 1H), 1.91-1.97 (m, 2H); ^{13}C-NMR (125 MHz, CD_3OD) δ 160.78, 160.13, 125.28, 122.03, 114.94, 111.02, 66.98, 62.66, 46.04, 30.67, 23.83; MS (ESI) calcd for $C_{11}H_{14}N_4O_2$ [M+H]: 235, found: [M+H]: 235, [M+Na]: 257.



Tces-guanidine 5.32: To a stirred solution of aminal **5.15** (170 mg, 0.890 mmol) and imidochloride **4.50** (TcesN=C(SMe)Cl) (342 mg, 1.07 mmol) in CH_2Cl_2 (9.0 mL) was added triethylamine (370 μL, 2.67 mmol) dropwise at 21 °C. The reaction mixture was stirred for 12 h and then concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 80% EtOAc/hexanes to EtOAc to give the isothiourea intermediate **5.32a** (420 mg, 99%).

The isothiourea **5.32a** (420 mg, 0.890 mmol) was dissolved in CH_3CN and the reaction mixture was charged with HMDS (460 μL, 2.23 mmol) and $HgCl_2$ (266 mg,

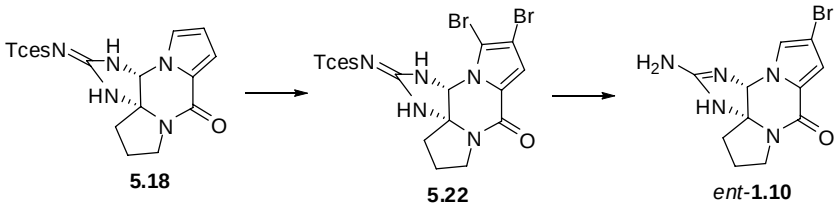
0.980 mmol) sequentially. After being stirred for 12 h at 21 °C, the reaction mixture was filtered to remove solid residue. The filtrate was concentrated *in vacuo* and purified by flash chromatography (silica gel, 80% EtOAc/hexanes to EtOAc) to give Tces-guanidine **5.32** as a white solid (230 mg, 59%): R_f = 0.26 (EtOAc); $[\alpha]_D$: +170.5 (*c* 0.15, 1:1 CH_3OH:CH_2Cl_2); IR (thin film) 3449, 3337, 2978, 1626 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD) δ 7.17 (dd, *J* = 1.5, 2.5 Hz, 1H), 6.84 (dd, *J* = 1.5, 4.0 Hz, 1H), 6.39 (d, *J* = 2.5 Hz, 1H), 6.23 (dd, *J* = 2.5, 4.0 Hz, 1H), 4.67-4.72 (dd, *J* = 11.5, 13.5 Hz, 2H), 4.29-4.33 (m, 1H), 3.73-3.78 (m, 1H), 3.50-3.55 (m, 1H), 2.22-2.27 (m, 1H), 2.10-2.16 (m, 1H), 1.96-2.03 (m, 1H), 1.85-1.92 (m, 1H); ^{13}C-NMR (125 MHz, CD_3OD) δ 160.10, 158.56, 125.52, 124.52, 114.55, 111.54, 95.59, 79.25, 62.24, 61.60, 45.33, 28.61, 24.01; MS (ESI) calcd for $C_{13}H_{16}Cl_3N_5O_4S$ [M+H]: 444, found: [M+H]: 444.



5.18 *ent*-**1.9**

(+)-Phakellin *ent*-1.9: To a solution of Tces-protected phakellin **5.18** (9.0 mg, 0.020 mmol) in MeOH/AcOH (0.15 mL/0.15 mL) was added zinc powder (7.0 mg, 0.10 mmol). The reaction mixture was heated to 40 °C and stirred vigorously for 30 min. The mixture was filtered through a cotton plug to remove zinc residue. Water (~10 mL) was added to the filtrate and the mixture was extracted with EtOAc (10 mL) to remove organic impurities. The aqueous phase was concentrated by lyophilization and the solid

residue was redissolved in 1.0 mL of water and purified by reversed phase prep-HPLC (C18 column, 0→90% CH_3CN/H_2O over 25 min, with 0.1% trifluoroacetic acid). The retention time of (+)-phakellin was 6 min. The fraction collected between 5.3-6.8 min was lyophilized to give (+)-phakellin (4.0 mg, 85%). Spectral data of synthetic (+)-phakellin correlated well with that reported previously (Chapter V, Table 9). (+)-Phakellin *ent*-**1.9**: R_f = 0 (EtOAc); $[\alpha]_D$: +5.6 (0.90, CH_3OH); IR (thin film) 3000-3500, 1697, 1552, 1383 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3CN) δ 7.19 (s, 1H), 6.91 (m, 1H), 6.40 (t, *J* = 3.5 Hz, 1H), 6.00 (s, 1H), 3.85 (m, 1H), 3.67 (m, 1H), 2.42 (m, 2H), 2.20 (m, 2H); ^{13}C-NMR (125 MHz, CD_3CN) δ 157.38, 154.02, 122.91, 122.86, 113.60, 112.13, 82.81, 68.25, 45.41, 38.73, 19.69; HRMS (ESI) Calcd for $C_{11}H_{13}N_5O$ [M+H]: 232.1198, found: 232.1191.

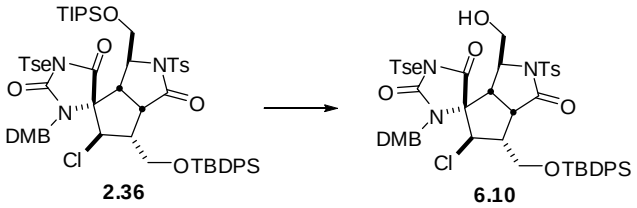


5.18 **5.22** ***ent*-1.10**

(+)-Monobromophakellin ***ent*-1.10**: To a solution of Tces-protected phakellin **5.18** (7.0 mg, 0.016 mmol) in CH_3CN (1.0 mL) was added NBS (6.0 mg, 0.032 mmol). The reaction mixture was stirred for 16 h at 21 °C, and then concentrated in *vacuo*. Column purification (silica gel, 70→80% EtOAc/hexanes) yielded the dibrominated product **5.22** (8.0 mg, 84%).

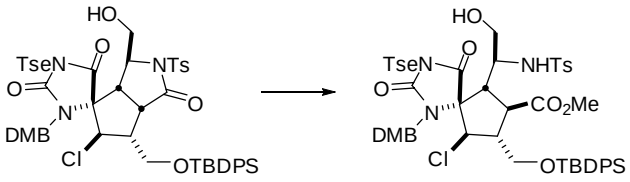
To a solution of the Tces-protected dibromophakellin **5.22** (6.0 mg, 0.010 mmol) in MeOH/AcOH (0.20 mL/0.10 mL) was added zinc powder (3.0 mg, 0.050 mmol). The reaction mixture was heated to 40 °C and stirred vigorously for 40 min. The mixture was filtered through a cotton plug to remove zinc residue and the filtrate was partitioned between water (10 mL) and EtOAc (10 mL). The aqueous phase was concentrated by lyophilization and the solid residue was redissolved in 1.0 mL of water and purified by reversed phase prep-HPLC (0→90% CH_3CN/H_2O over 25 min, with 0.1% trifluoroacetic acid). The solution collected between 8-10 min was lyophilized to give (+)-monobromophakellin *ent*-**1.10** (2.0 mg, 67%): R_f = 0 (EtOAc); $[\alpha]_D$: +118.3 (0.10, CH_3OH); IR (thin film) 3000-3500, 1634, 1244 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD) δ 7.24 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 6.03 (s, 1H), 3.84-3.88 (m, 1H), 3.62-3.68 (m, 1H), 2.41-2.45 (m, 2H), 2.17-2.21 (m, 2H), NH_2 and NH, NH^+ protons were not observed due to relatively large amount of H_2O; ^{13}C-NMR (125 MHz, CD_3OD) δ 157.21, 154.87, 124.93, 123.57, 116.12, 100.96, 84.04, 69.51, 46.87, 39.95, 20.69; HRMS (ESI) Calcd for $C_{11}H_{12}BrN_5O$ [M+H]: 310.0303, found: 310.0302.

Note: To compare directly with reported literature data, the synthetic (+)-monobromo-phakellin was treated with 0.01 M HCl in MeOH. Rotation and ^{1}H-NMR data were retaken and correlated well with literature values (Chapter V, Table 10).



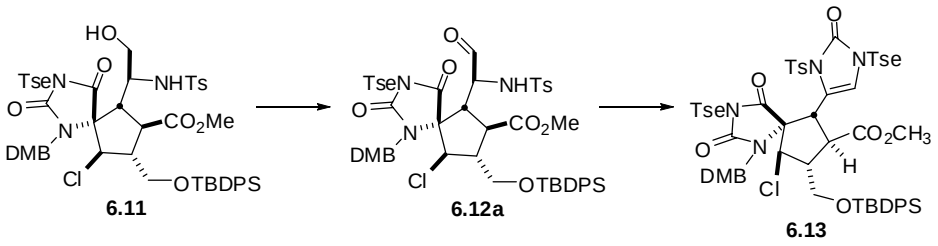
Alcohol 6.10: To a solution of chlorocyclopentane **2.36** (134 mg, 0.113 mmol) in anhydrous THF (2.0 mL) at -50 °C was added TBAF (1.0 M in THF, 136 μL, 0.136 mmol). The reaction mixture was stirred for 1 h at -50 ~ -40 °C. Upon completion of the reaction as indicated by TLC, the reaction was quenched with pH 7 buffer (5 mL) and partitioned between water (10 mL) and EtOAc (3 X 15 mL). The combined organics were washed with brine and dried further over Na_2SO_4. Column purification (silica gel, 30 → 50% EtOAc/Hexanes) after removal of solvents afforded TIPS-removed product **6.10** as a white foam (114 mg, 98%): R_f = 0.59 (60% EtOAc/Hexanes); $[\alpha]_D$ -26.1 (*c* 1.70, CH_2Cl_2); IR (thin film) 3063, 2932, 2856, 1717, 1652 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 8.14 (d, *J* = 8.0 Hz, 2H), 7.91 (m, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.80 (m, 2H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.21-7.29 (m, 6H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.37 (d, *J* = 8.0 Hz, 1H), 5.80 (d, *J* = 15.5 Hz, 1H), 4.79 (s, 1H), 4.71 (d, *J* = 16.0 Hz, 1H), 4.54 (d, *J* = 12.5 Hz, 1H), 4.45-4.49 (dd, *J* = 8.5, 10.5 Hz, 1H), 4.13-4.16 (dd, *J* = 4.0, 10.5 Hz, 1H), 3.93-3.96 (m, 1H), 3.72-3.74 (d, *J* = 11.5 Hz, 1H), 3.65-3.70 (m, 1H), 3.64 (s, 3H), 3.54-3.61 (m, 1H), 3.50 (d, *J* = 8.5 Hz, 1H), 3.40-3.46 (m, 2H), 3.29 (s, 3H), 3.19-3.24 (m, 1H), 2.94-2.99 (m, 1H), 1.86 (s, 3H), 1.76 (s, 3H), 1.17 (s, 9H), 0.99 (bs, 1H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 173.22, 171.85, 156.86, 150.30, 149.94, 145.07, 144.97, 136.34, 136.21, 136.01, 135.77, 134.12,

133.78, 130.06, 129.98, 129.92, 129.80, 129.59, 129.33, 128.95, 128.35, 121.58, 112.97, 112.14, 76.70, 63.75, 60.71, 60.57, 60.19, 55.81, 55.36, 50.82, 48.90, 48.13, 46.76, 46.04, 33.30, 27.23, 21.21, 19.58; MS (MALDI) calcd for $C_{52}H_{58}ClN_3O_{11}S_2Si$ [M+H]: 1028, [M+Na]: 1050, [M+K]: 1066; found [M+H]: 1028, [M+Na]: 1050, [M+K]: 1066.



Methyl ester 6.11: To a solution of alcohol **6.10** (80 mg, 0.078 mmol) in freshly distilled methanol (6.0 mL) was added potassium *tert*-butoxide (1.0 M solution in THF, 0.24 mL, 0.24 mmol) dropwise at 20 °C. The reaction was heated to 60 °C and stirred for 12 h. After 12 h, the reaction was quenched with pH 4 buffer (~ 5 mL) and the resulting mixture was partitioned between water (20 mL) and EtOAc (3 X 30 mL). The combined organics were washed with brine and dried further over Na_2SO_4. Column purification (silica gel, 50 → 70% EtOAc/Hexanes) after removal of solvents afforded epimerized methyl ester **6.11** as a colorless film (60 mg, 73%): R_f = 0.46 (60% EtOAc/Hexanes); $[\alpha]_D$ +26.0 (*c* 2.20, CH_2Cl_2); IR (thin film) 3511, 3271, 2934, 1776, 1717 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 7.83-7.86 (m, 4H), 7.80-7.82 (m, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.24-7.36 (m, 7H), 7.03-7.06 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.38 (d, *J* = 8.0 Hz, 1H), 5.76 (d, *J* = 9.5 Hz, 1H), 5.14 (d, *J* = 11.5 Hz, 1H), 4.88-4.96 (m, 2H), 4.16-4.20 (t, *J* = 11.0 Hz, 1H), 3.93-

3.97 (t, J = 11.5 Hz, 1H), 3.70-3.82 (m, 5H), 3.77 (s, 3H), 3.63 (s, 3H), 3.60-3.64 (m, 1H), 3.38-3.45 (m, 3H), 3.32 (s, 3H), 3.08-3.13 (m, 1H), 2.74-2.79 (t, J = 11.5 Hz, 1H), 1.91 (s, 3H), 1.84 (s, 3H), 1.25 (s, 9H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 174.70, 173.28, 157.38, 150.35, 149.61, 144.86, 142.86, 139.64, 136.16, 136.07, 135.68, 133.94, 133.12, 130.27, 130.17, 130.10, 129.87, 128.99, 128.94, 128.35, 128.31, 127.03, 120.39, 112.23, 111.67, 74.49, 62.01, 60.45, 58.04, 55.63, 55.28, 54.91, 52.55, 52.50, 49.55, 48.48, 46.59, 46.21, 33.54, 27.31, 21.20, 19.78; MS (MALDI) calcd for $C_{53}H_{62}ClN_3O_{12}S_2Si$ [M+Na]: 1082, [M+K]: 1098; found [M+Na]: 1082, [M+K]: 1098.

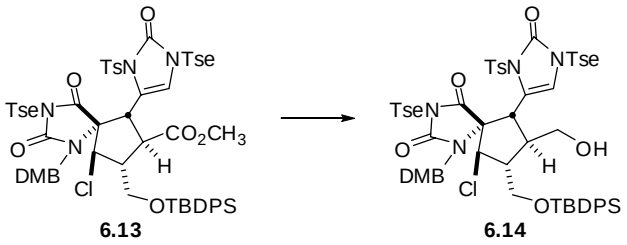


Imidazolone 6.13: To a solution of alcohol **6.11** (47 mg, 0.044 mmol) in CH_2Cl_2 (3.0 mL) was added Dess-Martin periodinane (56 mg, 0.13 mmol), and the resulting reaction mixture was stirred at 20 °C for 5 h. Upon completion of the reaction as indicated by TLC, anhydrous ether (Et_2O, ~20 mL) was added to the reaction mixture and the solid residue was removed by filtration through Celite. Removal of solvents *in vacuo* afforded the aldehyde **6.12a** (47 mg, 99%).

A portion of the aldehyde **6.12a** (7.0 mg, 0.0066 mmol) obtained above was dissolved in anhydrous CH_2Cl_2 (0.6 mL) and cooled to 0 °C. To the solution was added

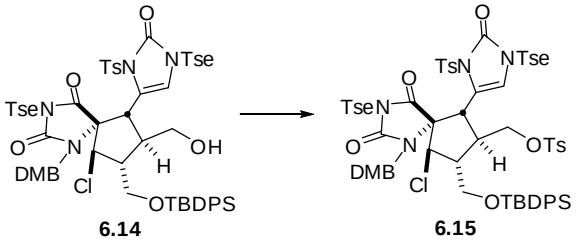
$MgSO_4$ (~10 mg) and $TseNH_2$ (2.0 mg, 0.010 mmol). The reaction mixture was warmed to 20 °C and stirred for 40 min. Removal of $MgSO_4$ solid residue by filtration and concentration *in vacuo* yielded the Tse-imine intermediate **6.12**, which was used directly for next step without purification. The Tse-imine **6.12** was dissolved in anhydrous THF (0.6 mL) and cooled to 0 °C. To the solution was added Et_3N (4 μL, 0.028 mmol) and triphosgene (~ 5 mg, 0.017 mmol) sequentially. The reaction mixture was warmed to 20 °C and stirred for 20 min, then it was heated to 60 °C and stirred for 2.5 h. Upon completion of the reaction time, sat'd $NaHCO_3$ solution (2 mL) was added, and the resulting mixture was partitioned between water (10 mL) and EtOAc (2 X 10 mL). The combined organics were washed with brine, dried further over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, 40 → 60% EtOAc/Hexanes) afforded imidazolone **6.13** as a colorless film (5.2 mg, 63% over three steps): R_f = 0.63 (60% EtOAc/Hexanes); $[\alpha]_D$ -44.7 (*c* 0.75, CH_2Cl_2); IR (thin film) 2955, 1723, 1640 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 8.18 (d, *J* = 8.0 Hz, 2H), 7.72-7.75 (m, 4H), 7.66-7.68 (m, 2H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.23-7.33 (m, 7H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 1.5 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 2H), 6.63 (d, *J* = 8.0 Hz, 2H), 6.40 (d, *J* = 8.0 Hz, 1H), 5.45-5.50 (m, 2H), 4.92 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 16.5 Hz, 1H), 4.33-4.38 (m, 1H), 4.11-4.17 (m, 1H), 3.78-3.92 (m, 4H), 3.69-3.74 (m, 1H), 3.68 (s, 3H), 3.36-3.41 (m, 1H), 3.34 (s, 3H), 3.28 (s, 3H), 3.19-3.26 (m, 2H), 2.83-2.88 (m, 1H), 2.32-2.36 (m, 1H), 1.81 (s, 3H), 1.79 (s, 3H), 1.74 (s, 3H), 1.23 (s, 9H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 173.66, 171.74, 157.28, 150.72, 150.17, 149.36, 145.44, 144.61, 143.88, 136.78, 136.61, 136.00, 135.78, 134.62, 133.35, 133.05,

130.34, 130.18, 130.12, 129.85, 129.79, 129.63, 129.29, 128.57, 128.21, 120.66, 118.64, 115.40, 112.51, 111.69, 73.34, 59.82, 58.28, 55.65, 55.13, 54.08, 53.24, 51.99, 47.07, 44.48, 43.93, 43.19, 37.05, 34.19, 30.08, 27.21, 27.15, 21.05, 21.03, 21.01, 19.58; HRMS (ESI) calcd for $C_{63}H_{69}ClN_4O_{14}S_3Si$ [M+Li]: 1271.3590; found [M+Li]: 1271.3604.



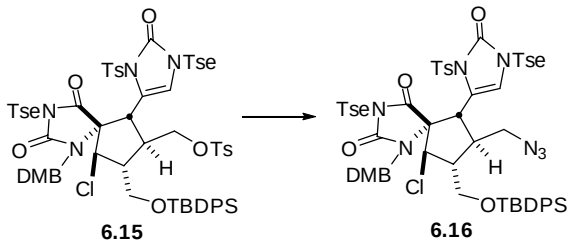
Alcohol 6.14: To a solution of imidazolone **6.13** (15 mg, 0.012 mmol) in CH_2Cl_2 (1.0 mL) at -78 °C was added DIBAl-H (~40 μL, 0.22 mmol). The reaction mixture was stirred at -78 °C for 30 min and then quenched with Rochelle's salt solution (~2 mL) at -78 °C, warmed to 20 °C and stirred vigorously for 3 h. Then the mixture was transferred into a separation funnel and partitioned between water and CH_2Cl_2. The organic layer was washed with brine and dried further over Na_2SO_4. After removal of solvent *in vacuo*, alcohol **6.14** was obtained in high purity as a foam (15mg, 99%): R_f = 0.24 (60% EtOAc/Hexanes); $[\alpha]_D$ -20.7 (*c* 0.63, CH_2Cl_2); IR (thin film) 3520, 2931, 2857, 1774, 1717 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 8.11 (d, *J* = 8.0 Hz, 2H), 7.75-7.77 (m, 2H), 7.69-7.71 (m, 4H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.21-7.33 (m, 7H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.66 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 2H), 6.59 (d,

J = 1.5 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 5.19 (d, *J* = 16.5 Hz, 1H), 4.86 (d, *J* = 11.5 Hz, 1H), 4.79 (d, *J* = 10.0 Hz, 1H), 4.59 (d, *J* = 16.0 Hz, 1H), 4.32-4.38 (m, 1H), 4.12-4.18 (m, 1H), 3.85-3.94 (m, 2H), 3.74-3.80 (m, 2H), 3.68-3.72 (m, 2H), 3.67 (s, 3H), 3.51-3.54 (m, 2H), 3.34 (s, 3H), 2.85-2.89 (m, 1H), 2.73-2.79 (m, 2H), 2.56-2.61 (m, 1H), 2.40-2.50 (bs, 1H), 1.82 (s, 3H), 1.80 (s, 3H), 1.78 (s, 3H), 1.22 (s, 9H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 174.19, 157.42, 150.71, 150.01, 149.26, 145.41, 144.63, 144.00, 136.80, 136.58, 136.04, 135.86, 134.95, 133.35, 133.07, 130.31, 130.29, 130.17, 129.84, 129.71, 129.05, 128.43, 128.29, 120.65, 119.67, 115.57, 112.41, 111.90, 74.33, 62.54, 60.16, 59.17, 55.69, 55.25, 54.04, 53.29, 45.87, 44.75, 42.83, 42.44, 37.22, 34.02, 30.08, 27.24, 21.08, 21.06, 21.03, 18.51; HRMS (MALDI) calcd for $C_{62}H_{69}ClN_4O_{13}S_3Si$ [M+H]: 1237.3559, [M+Na]: 1259.3379, [M+K]: 1275.3118; found [M+H]: 1237.3911, [M+Na]: 1259.4053, [M+K]: 1275.3740.



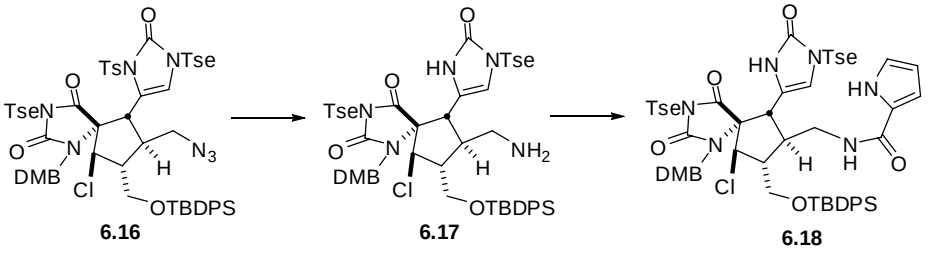
Tosylate 6.15: To a mixture of alcohol **6.14** (10 mg, 0.0081 mmol) and TsCl (3 mg, 0.016 mmol) was added anhydrous CH_2Cl_2 (0.50 mL), followed by triethylamine (4 μL, 0.032 mmol) and a few crystals of DMAP. The reaction mixture was stirred vigorously at 20 °C. Upon completion of the reaction as indicated by TLC (~3 h), the reaction

mixture was quenched with pH 7 buffer (~ 3 mL) and partitioned between water (10 mL) and EtOAc (15 mL). The organic layer was washed with brine, and dried further over Na_2SO_4. After removal of solvents *in vacuo*, the residue was purified by column chromatography (silica gel, 40 → 50% EtOAc/Hexane) to afford tosylate **6.15** as a colorless foam (8 mg, 73%): R_f = 0.40 (60% EtOAc/Hexanes); IR (thin film) 2958, 2857, 1774, 1723 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 8.23 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.69 (m, 4H), 7.60-7.62 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.20-7.35 (m, 7H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.70 (s, 1H), 6.68 (d, *J* = 8.0 Hz, 2H), 6.66 (d, *J* = 8.0 Hz, 2H), 6.46 (d, *J* = 8.0 Hz, 1H), 5.37 (d, *J* = 16.0 Hz, 1H), 4.87 (d, *J* = 10.0 Hz, 1H), 4.80 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 16.0 Hz, 1H), 4.31-4.37 (m, 2H), 4.08-4.15 (m, 2H), 3.83-3.89 (m, 1H), 3.71-3.78 (m, 2H), 3.65 (s, 3H), 3.52-3.62 (m, 2H), 3.38 (d, *J* = 9.5 Hz, 1H), 3.31 (s, 3H), 2.94-3.04 (m, 2H), 2.70 (t, *J* = 11.0 Hz, 1H), 2.55-2.60 (m, 1H), 1.90 (s, 3H), 1.83 (s, 3H), 1.81 (s, 3H), 1.77 (s, 3H), 1.17 (s, 9H); ^{13}C-NMR (125 MHz, benzene-d_6) δ = 173.30, 157.09, 150.76, 150.04, 149.33, 145.66, 144.93, 144.65, 144.02, 136.69, 136.56, 135.95, 135.75, 134.70, 133.29, 133.01, 132.89, 130.36, 130.27, 130.20, 130.03, 129.89, 129.84, 129.31, 128.45, 128.37, 128.21, 128.15, 120.84, 118.72, 115.50, 112.76, 111.66, 74.07, 68.91, 59.58, 58.32, 55.65, 55.18, 54.18, 53.27, 45.19, 44.54, 43.11, 39.19, 37.24, 34.03, 30.07, 27.21, 27.14, 21.14, 21.09, 21.07, 21.04, 19.41; MS (MALDI) calcd for $C_{69}H_{75}ClN_4O_{15}S_4Si$ [M+H]: 1391, [M+Na]: 1413, [M+K]: 1429; found [M+H]: 1391, [M+Na]: 1413, [M+K]: 1429.



Azide 6.16: To the tosylate **6.15** (40 mg, 0.029 mmol) in a dry flask equipped with a septum was added NaN_3 (19 mg, 0.29 mmol) and anhydrous DMF (3.0 mL). The septum was replaced by a yellow polyethylene stopper, and then the reaction mixture was heated to 50 °C and stirred for 12 h, after which the reaction mixture was partitioned between water (10 mL) and EtOAc (15 mL). The organic layer was washed with water, brine, and dried over Na_2SO_4. After removal of solvents *in vacuo*, the residue was purified by column chromatography (silica gel, 50 → 60% EtOAc/Hexane) to afford azide **6.16** as a light-yellow foam (29 mg, 81%): R_f = 0.49 (60% EtOAc/Hexanes); $[\alpha]_D$ -12.8 (*c* 1.20, CH_2Cl_2); IR (thin film) 2931, 2857, 2102, 1774, 1720 cm^{-1}; ^{1}H-NMR (500 MHz, benzene-d_6) δ = 8.06 (d, *J* = 8.0 Hz, 2H), 7.68-7.70 (m, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.58-7.60 (m, 2H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.21-7.30 (m, 7H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.59 (d, *J* = 8.0 Hz, 4H), 6.56 (d, *J* = 1.0 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 5.26 (d, *J* = 16.5 Hz, 1H), 4.80 (d, *J* = 11.0 Hz, 1H), 4.51 (d, *J* = 8.5 Hz, 1H), 4.45 (d, *J* = 16.5 Hz, 1H), 4.30-4.36 (m, 1H), 4.07-4.13 (m, 1H), 3.80-3.86 (m, 2H), 3.67-3.73 (m, 1H), 3.64 (s, 3H), 3.51 (d, *J* = 11.0 Hz, 1H), 3.44-3.47 (m, 2H), 3.29 (s, 3H), 3.01-3.09 (m, 2H), 2.75-2.80 (m, 1H), 2.66-2.70 (m, 2H), 2.39 (dt, *J* = 14.5, 5.0 Hz, 1H), 1.76 (s, 3H), 1.74 (s, 3H), 1.70 (s, 3H), 1.19 (s, 9H); ^{13}C-NMR (125 MHz, benzene-

d_6) δ = 173.82, 157.32, 150.64, 150.08, 149.38, 145.62, 144.60, 143.95, 136.79, 136.61, , 136.02, 135.85, 134.86, 133.07, 133.06, 130.39, 130.29, 130.22, 129.82, 129.81, 129.66, 129.12, 128.48, 128.33, 128.20, 128.01, 127.83, 120.88, 119.03, 115.25, 112.75, 111.78, 74.24, 59.55, 58.36, 55.69, 55.21, 53.99, 53.27, 52.92, 46.38, 44.63, 44.36, 39.16, 37.25, 34.09, 30.08, 27.25, 27.18, 21.05, 21.04, 21.01, 19.45; MS (MALDI) calcd for $C_{62}H_{68}ClN_7O_{12}S_3Si$ [M+Na]: 1284, [M+K]: 1300; found [M+Na]: 1284, [M+K]: 1300.



Pyrrole-imidazolone 6.18: To a solution of azide **6.16** (15 mg, 0.012 mmol) in THF (0.40 mL) was added SmI_2 (0.1 M solution in THF, 0.95 mL, 0.095 mmol) at -78 °C. The reaction was warmed to 20 °C and stirred for 15 min, and then quenched with saturated $NaHCO_3$ (4 mL) and the resulting mixture was partitioned between water (~10 mL) and EtOAc (2 X 10 mL). The combined organic layers were washed with brine, and then dried over Na_2SO_4. Removal of solvent *in vacuo* afforded primary amine **6.17** quantitatively with sufficient purity for subsequent reaction.

To a solution of amine **6.17** (13 mg, 0.012 mmol) and pyrrole-2-carbonyl chloride (16 mg, 0.12 mmol) in anhydrous methylene chloride (1.0 mL) was added triethylamine (17 μL, 0.12 mmol) at 0 °C. The reaction mixture was warmed to 20 °C

and stirred for 15 min, after which it was partitioned between $NaHCO_3$ solution (~10 mL) and EtOAc (2 X10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After concentration *in vacuo*, purification by flash chromatography (silica gel, EtOAc) afforded pyrrole-imidazolone **6.18** as a colorless film (9 mg, 64% over two steps): R_f = 0.18 (EtOAc); IR (thin film) 3381, 2931, 1771, 1714, 1682 cm^{-1}; MS (MALDI) calcd for $C_{60}H_{67}ClN_6O_{11}S_2Si$ [M+H]: 1175, [M+Na]: 1197, [M+K]: 1213; found [M+H]: 1175, [M+Na]: 1197, [M+K]: 1213.

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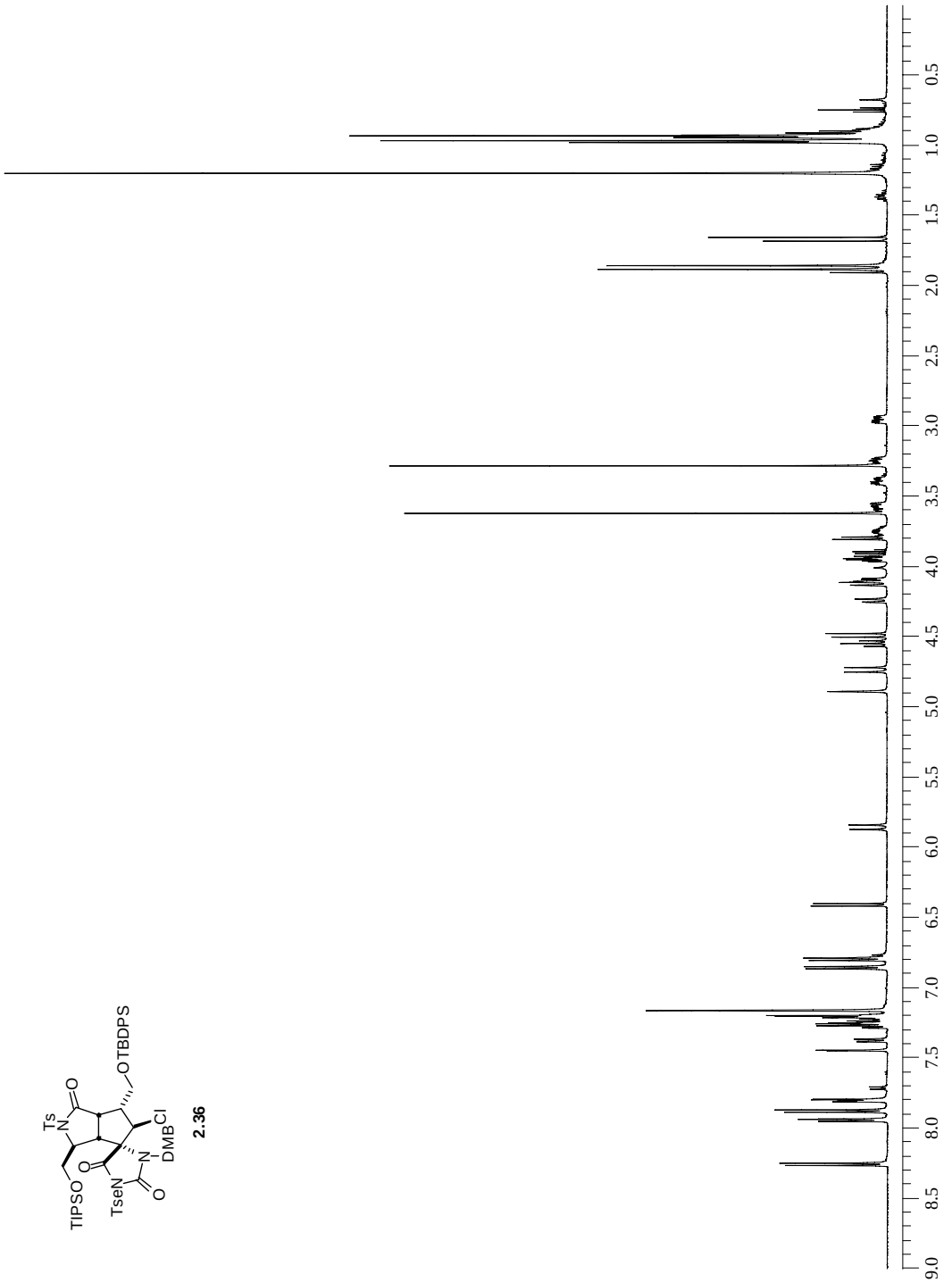
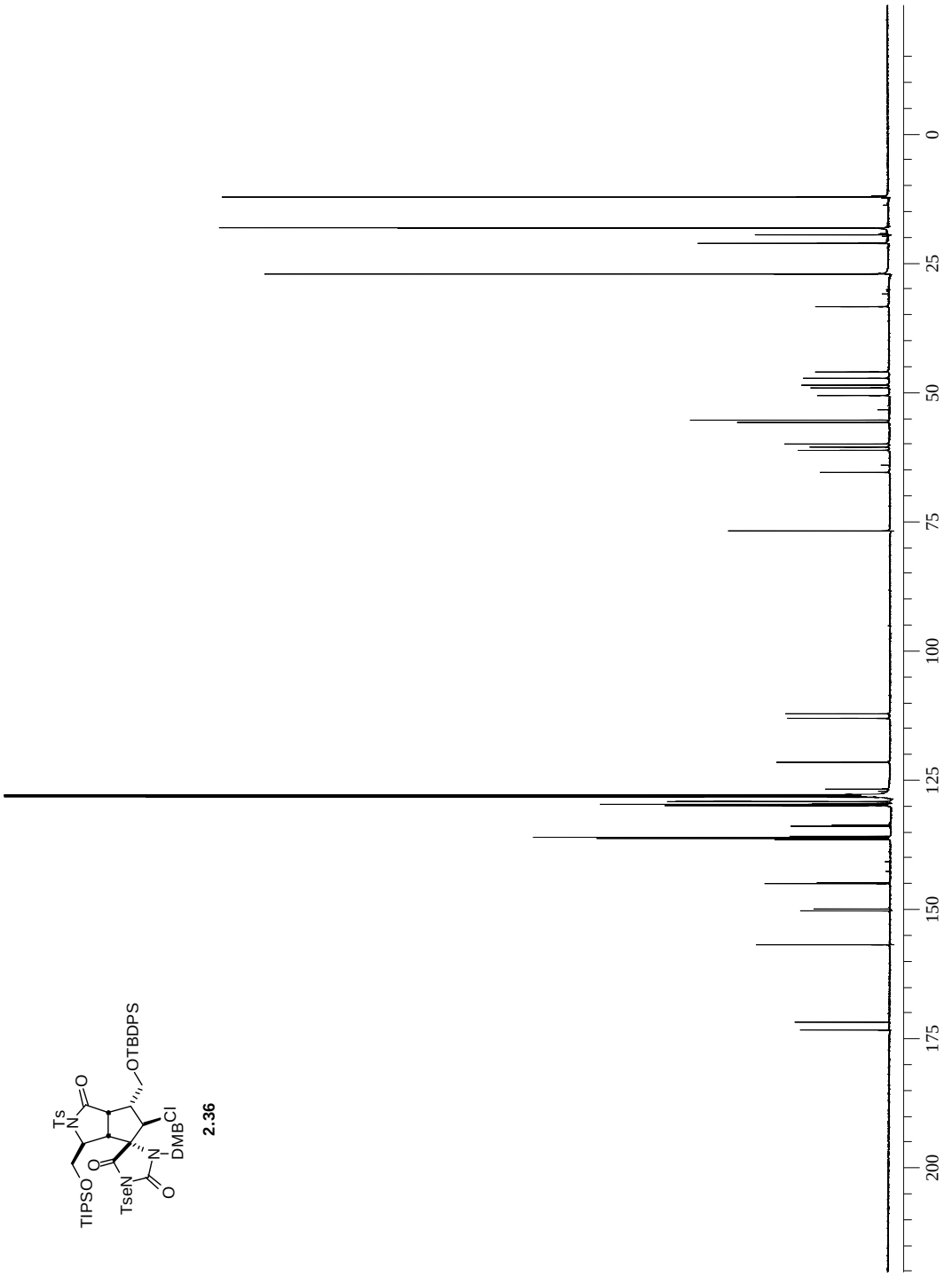
APPENDIX A

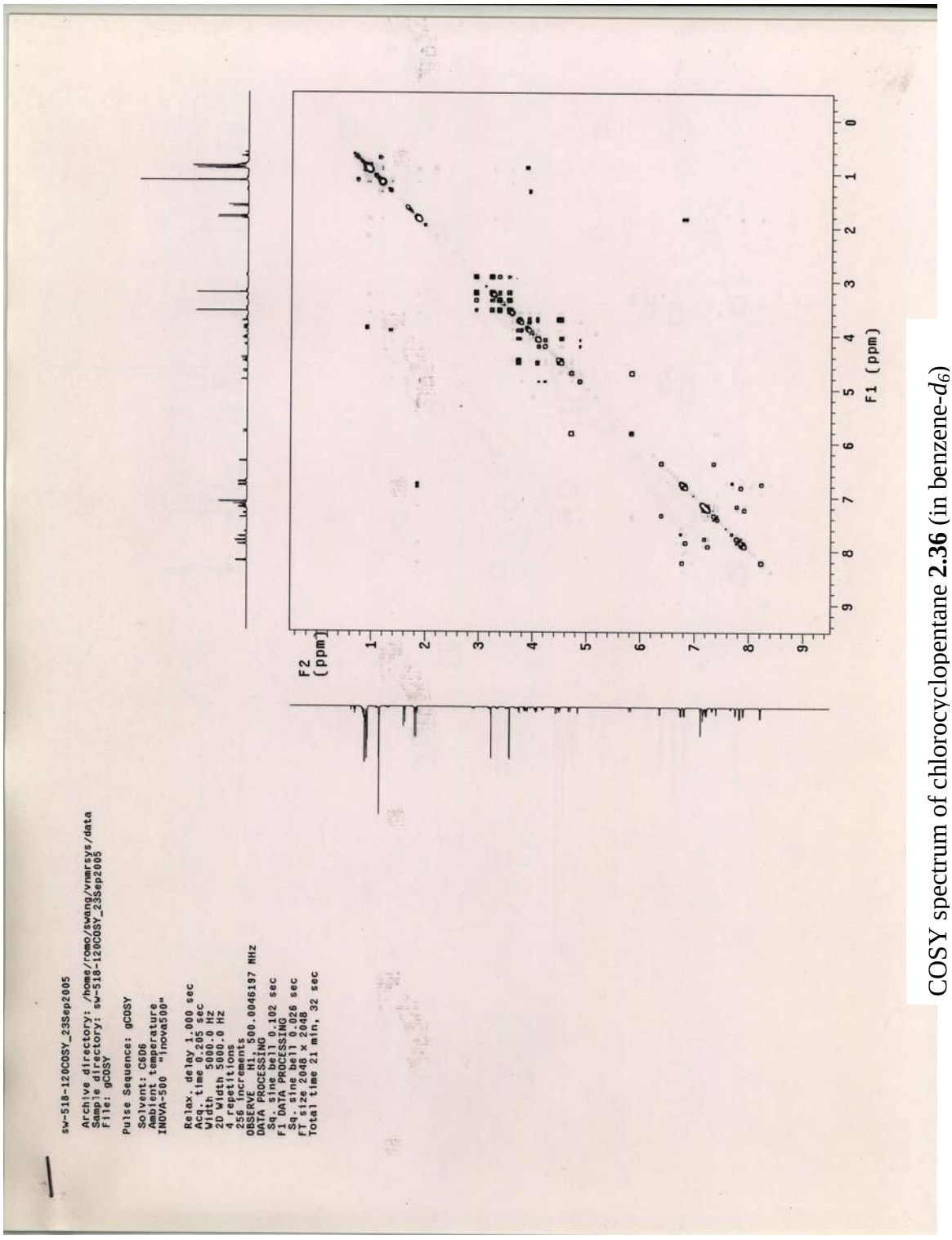
SELECTED SPECTRA DATA



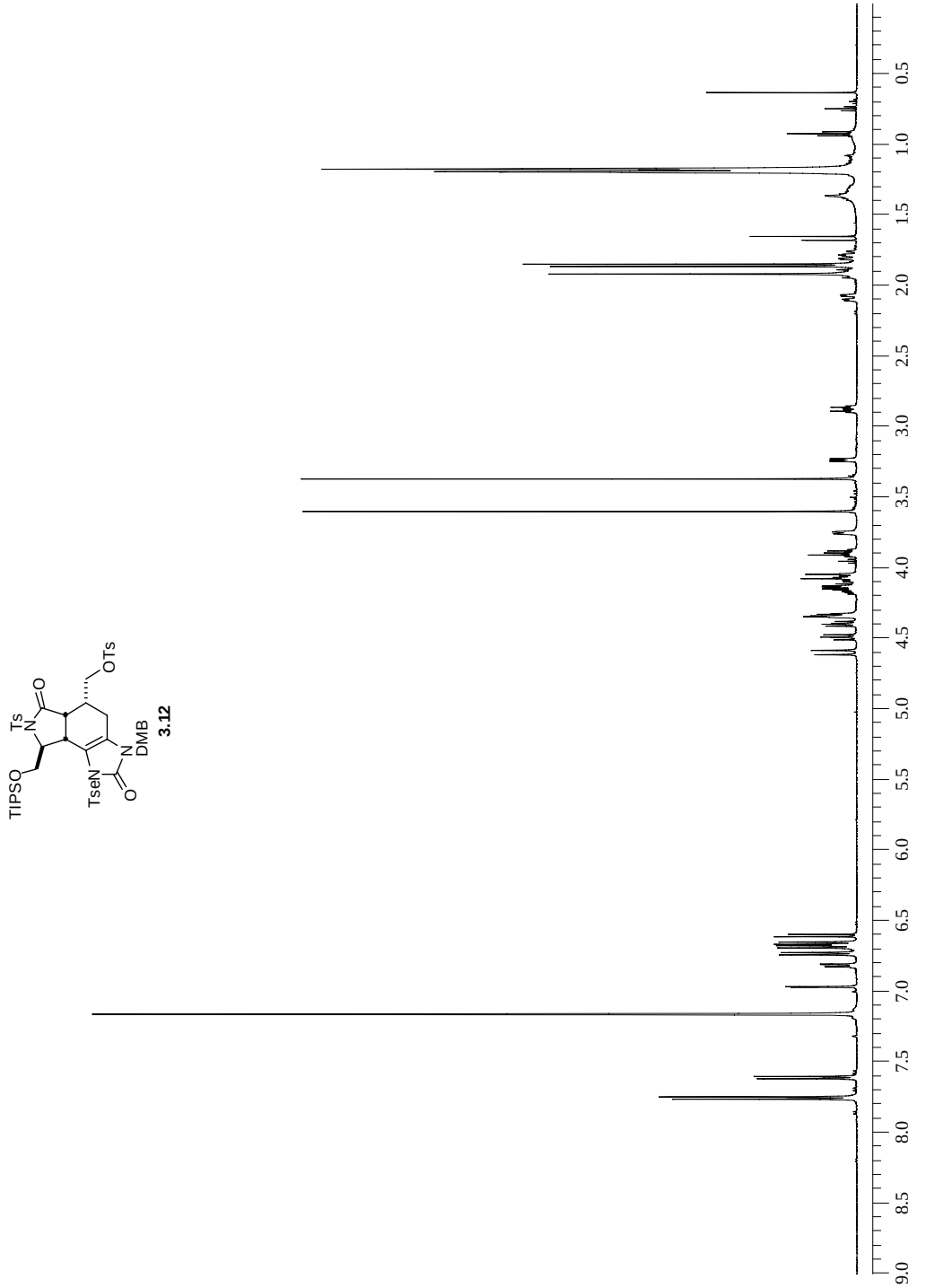
^{1}H-NMR spectrum of chlorocyclopentane **2.36** (in benzene-d_6)



^{13}C-NMR spectrum of chlorocyclopentane **2.36** (in benzene-d_6)



COSY spectrum of chlorocyclopentane **2.36** (in benzene-d_6)



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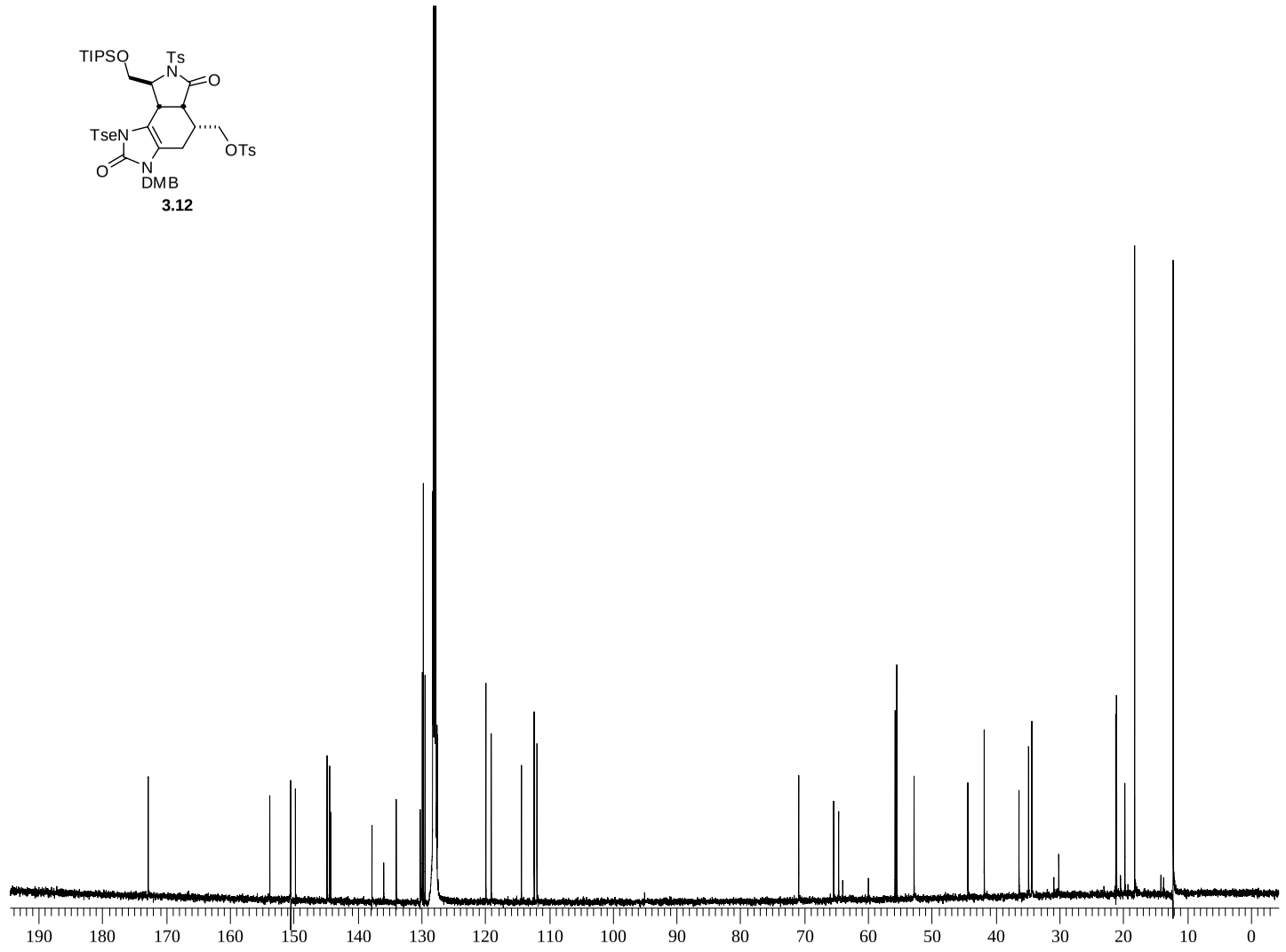
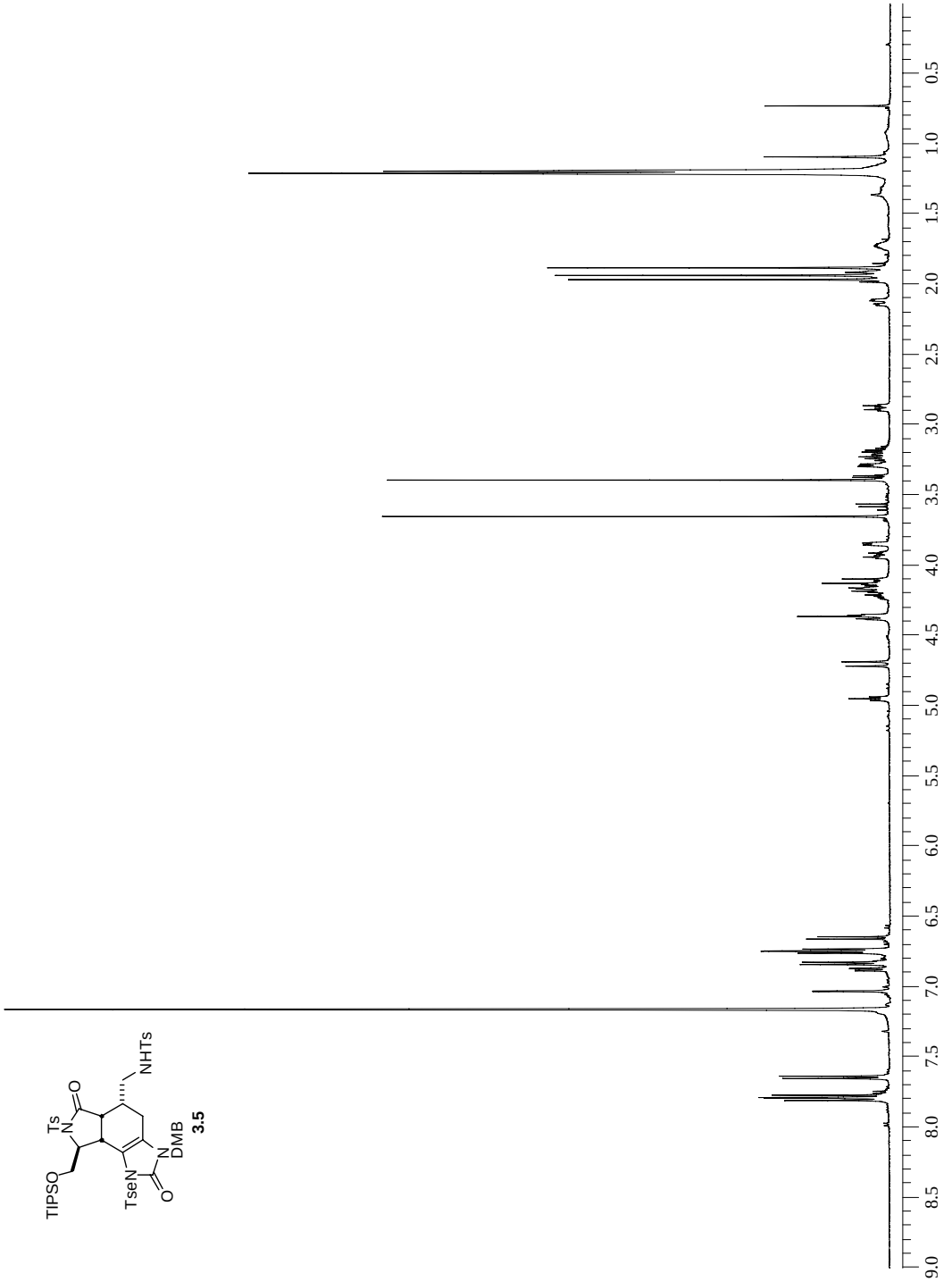
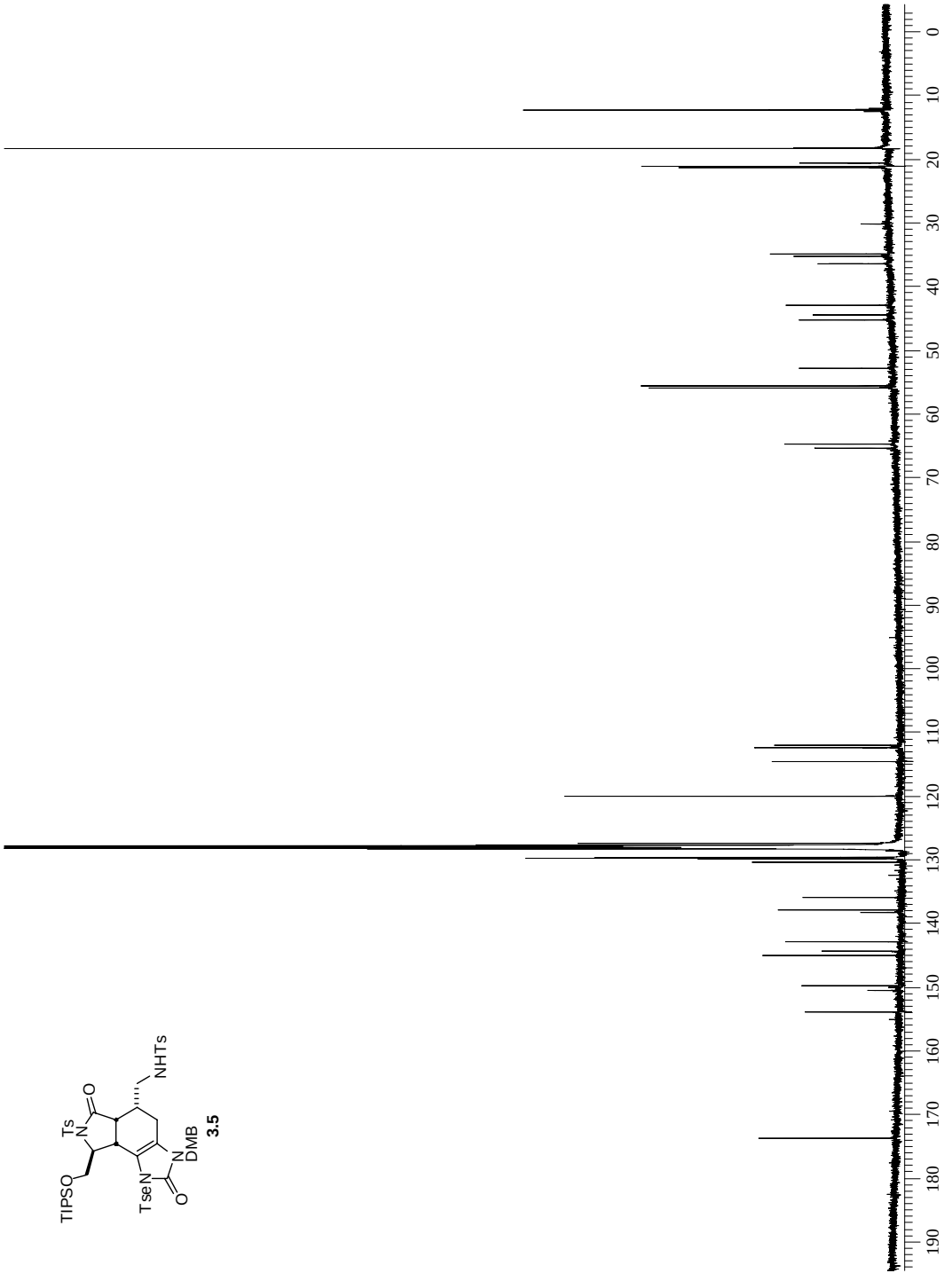


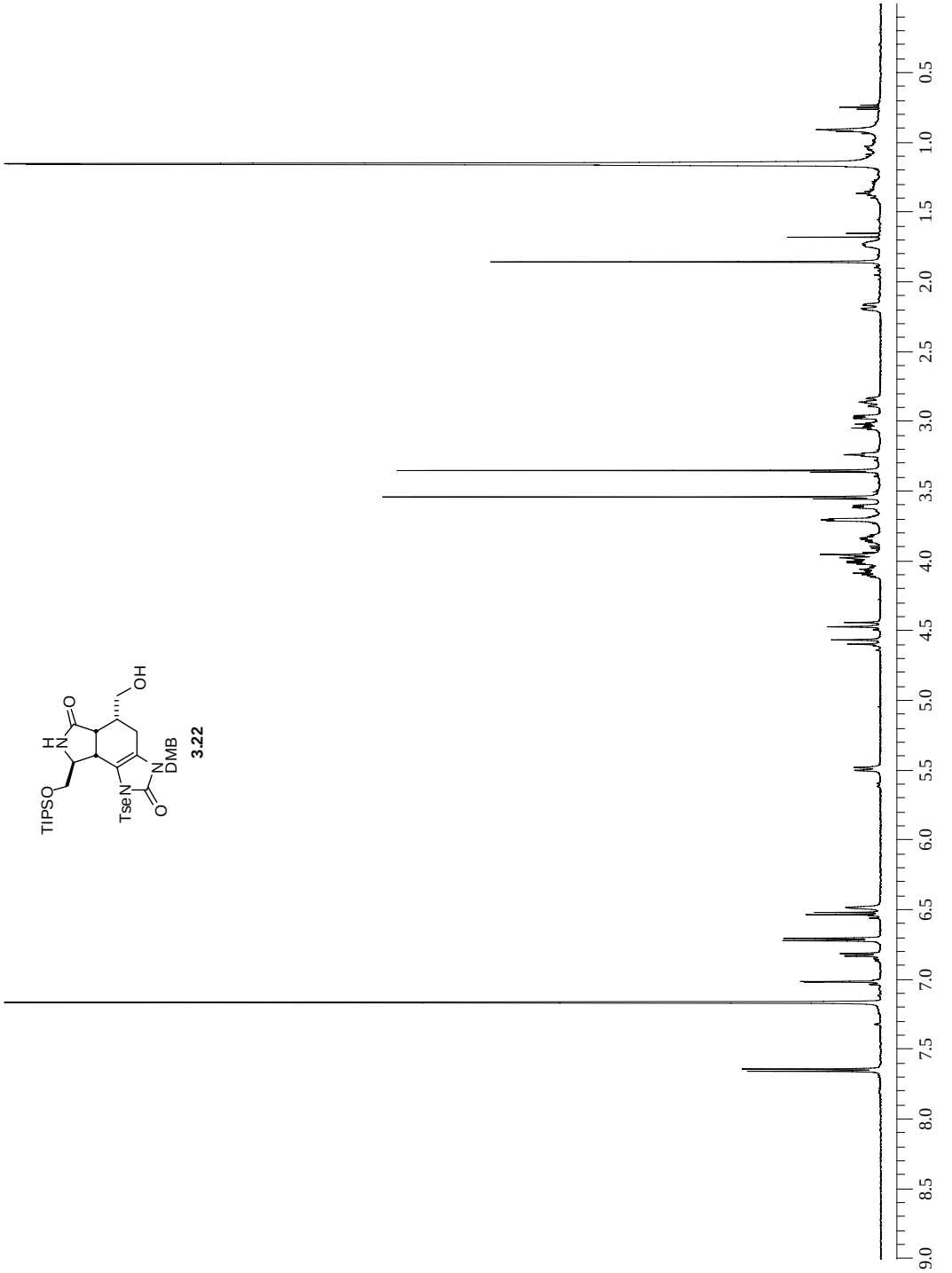
^{13}C-NMR spectrum of tosylate **3.12** (in benzene-d_6)



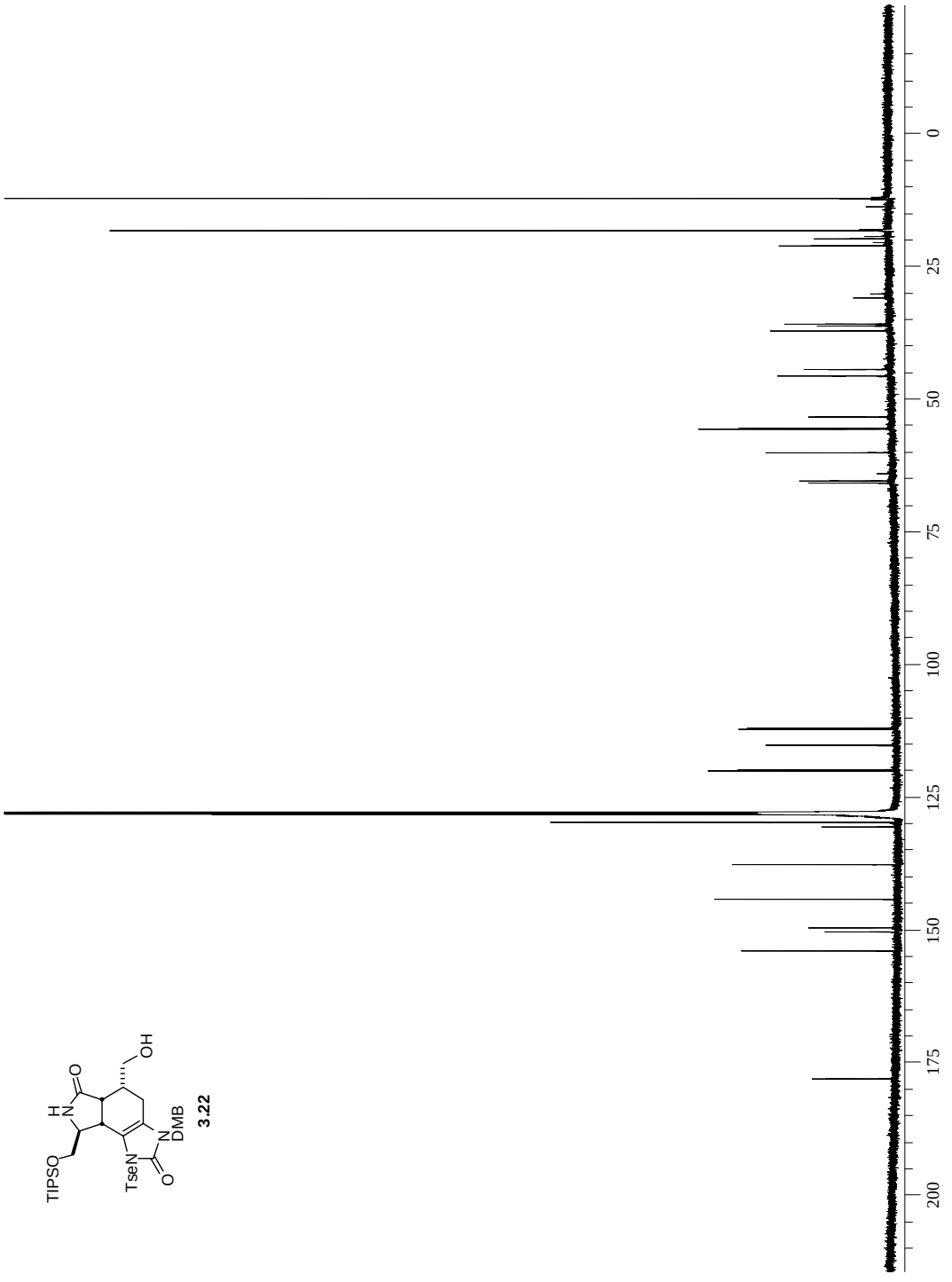
^{1}H-NMR spectrum of sulfonamide **3.5** (in benzene-d_6)



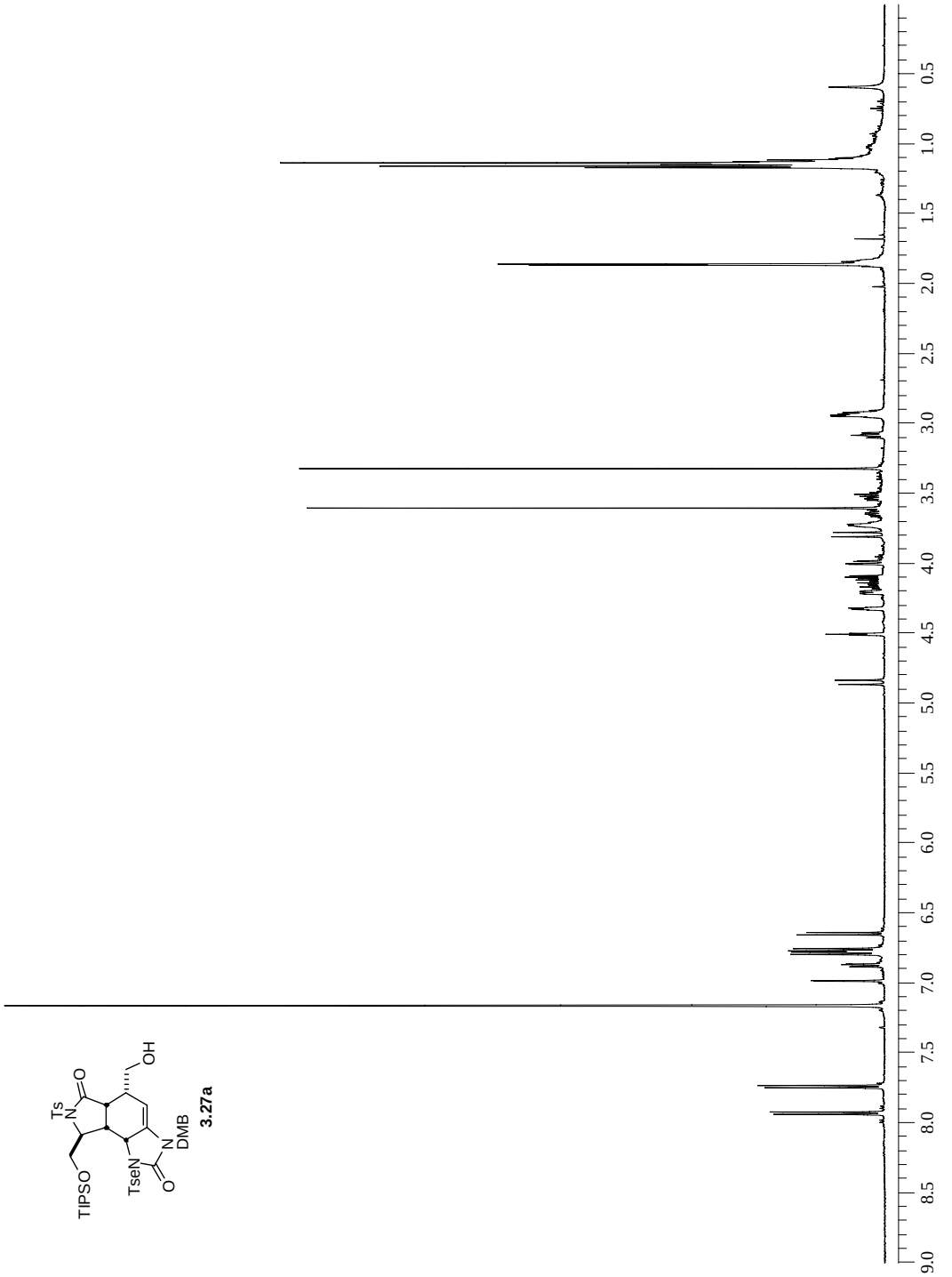
^{13}C-NMR spectrum of sulfonamide **3.5** (in benzene-d_6)



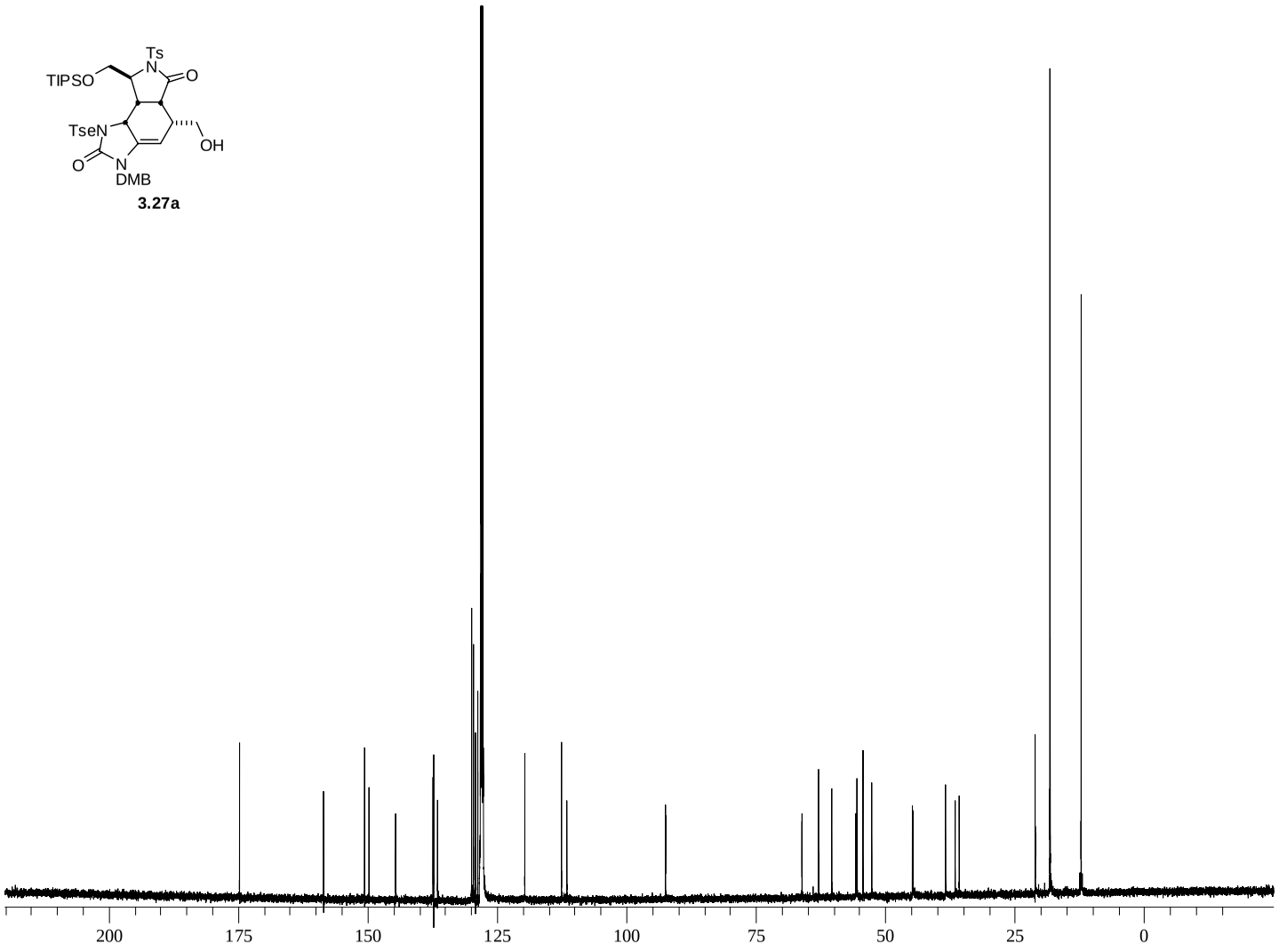
^{1}H-NMR spectrum of lactam **3.22** (in benzene-d_6)



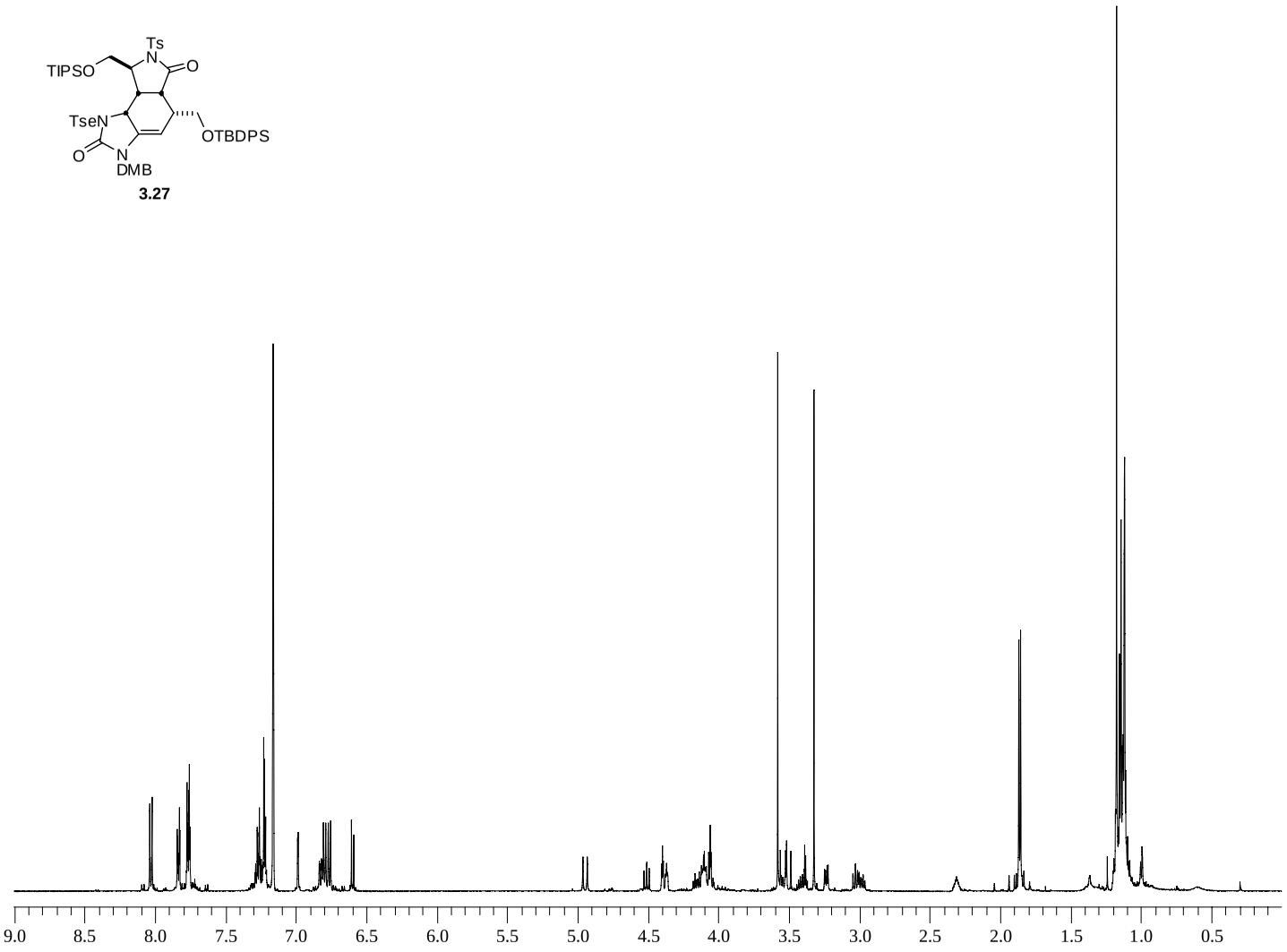
^{13}C-NMR spectrum of lactam **3.22** (in benzene-d_6)



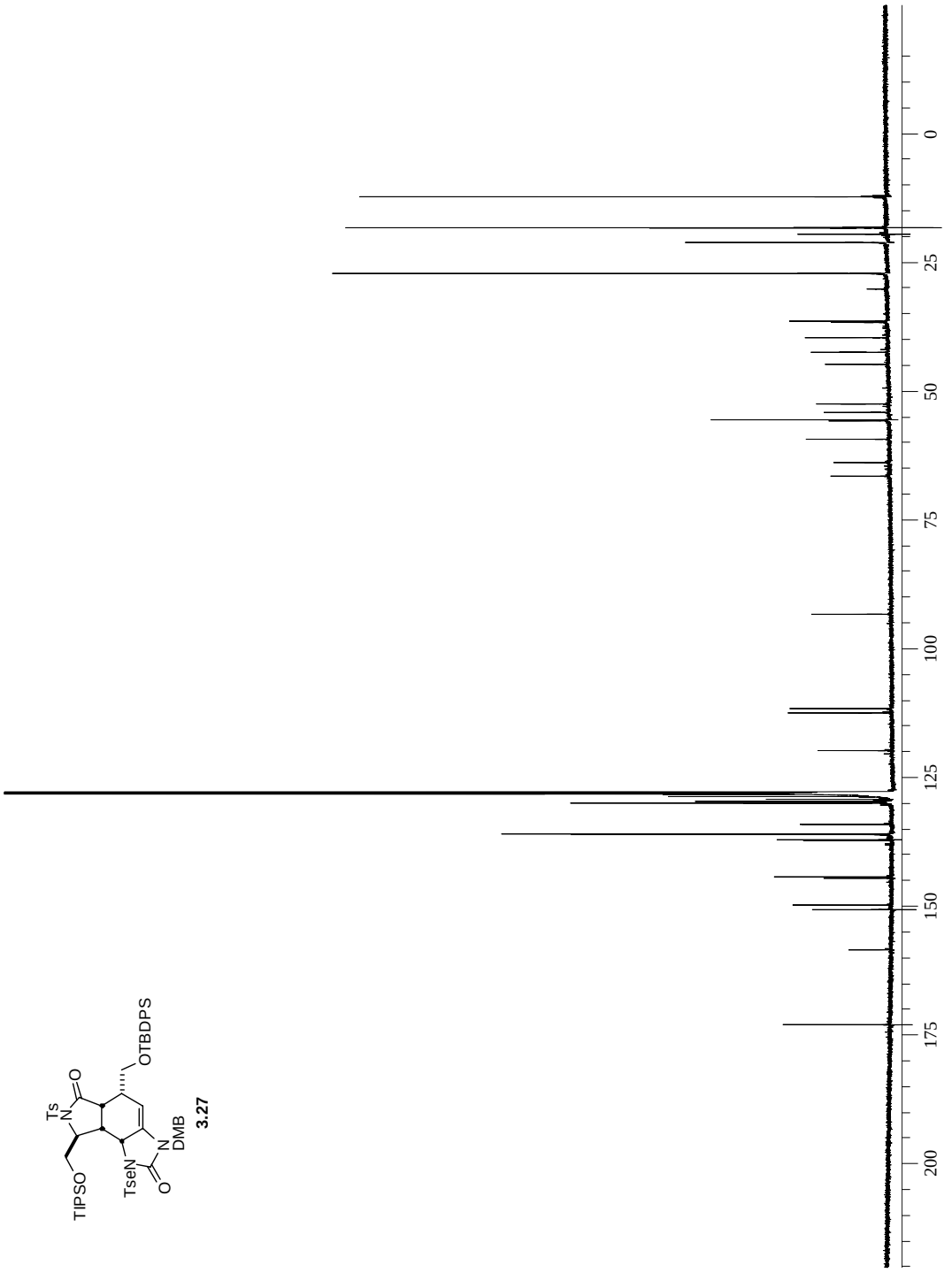
^{1}H-NMR spectrum of Diels-Alder adduct **3.27a** (in benzene-d_6)



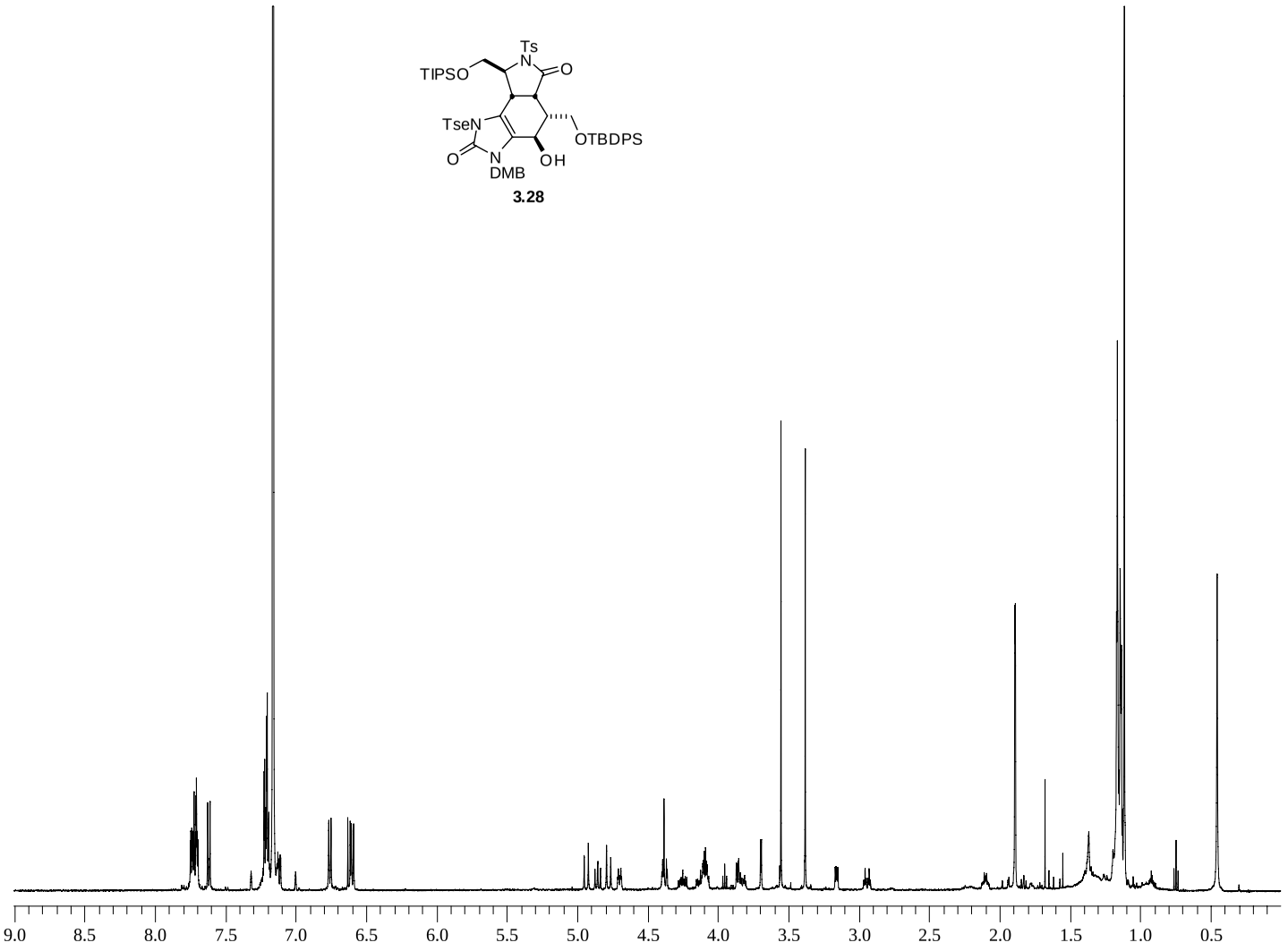
^{13}C-NMR spectrum of Diels-Alder adduct **3.27a** (in benzene-d_6)



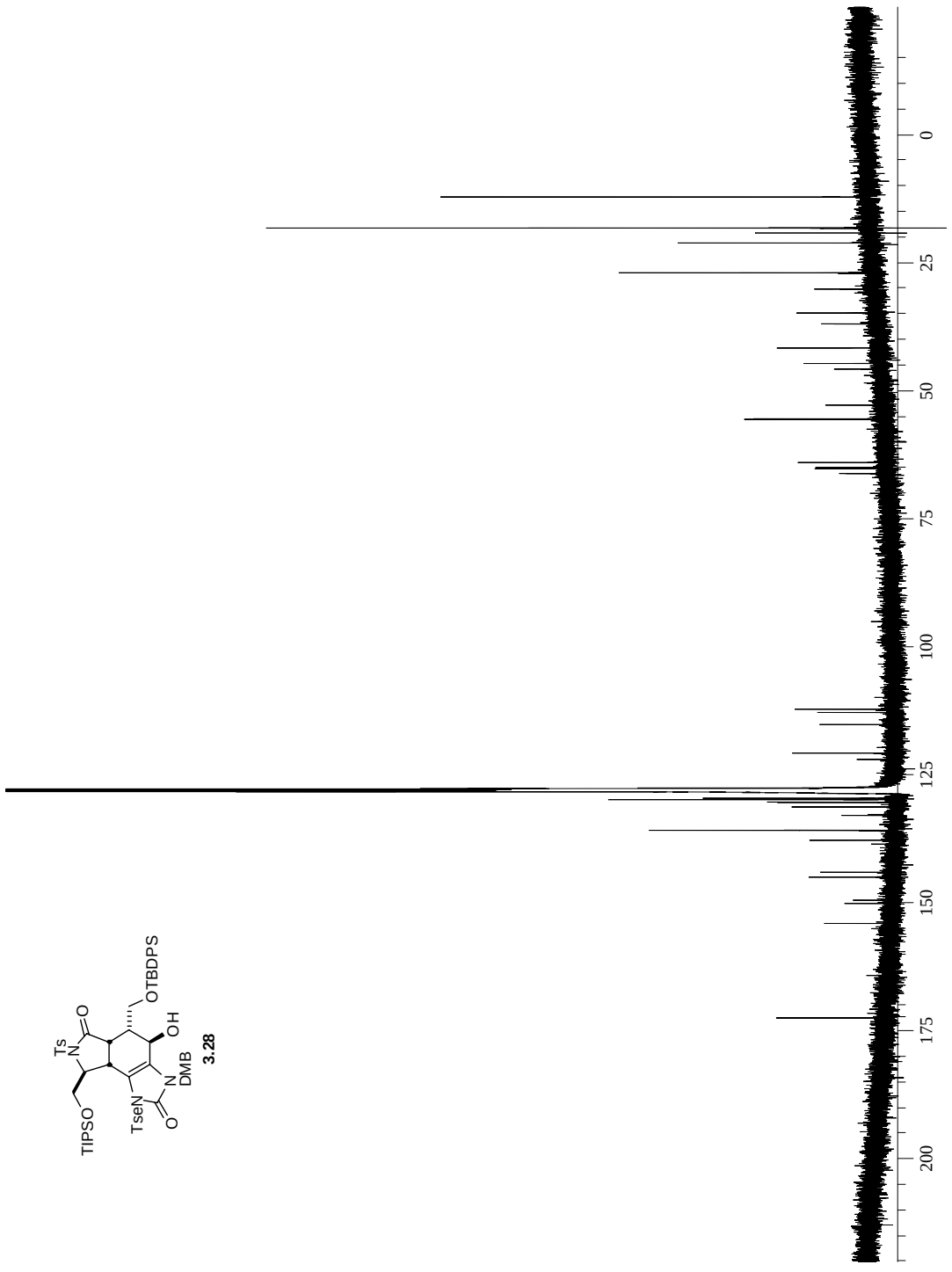
^{1}H-NMR spectrum of TBDPS silylether **3.27** (in benzene-d_6)



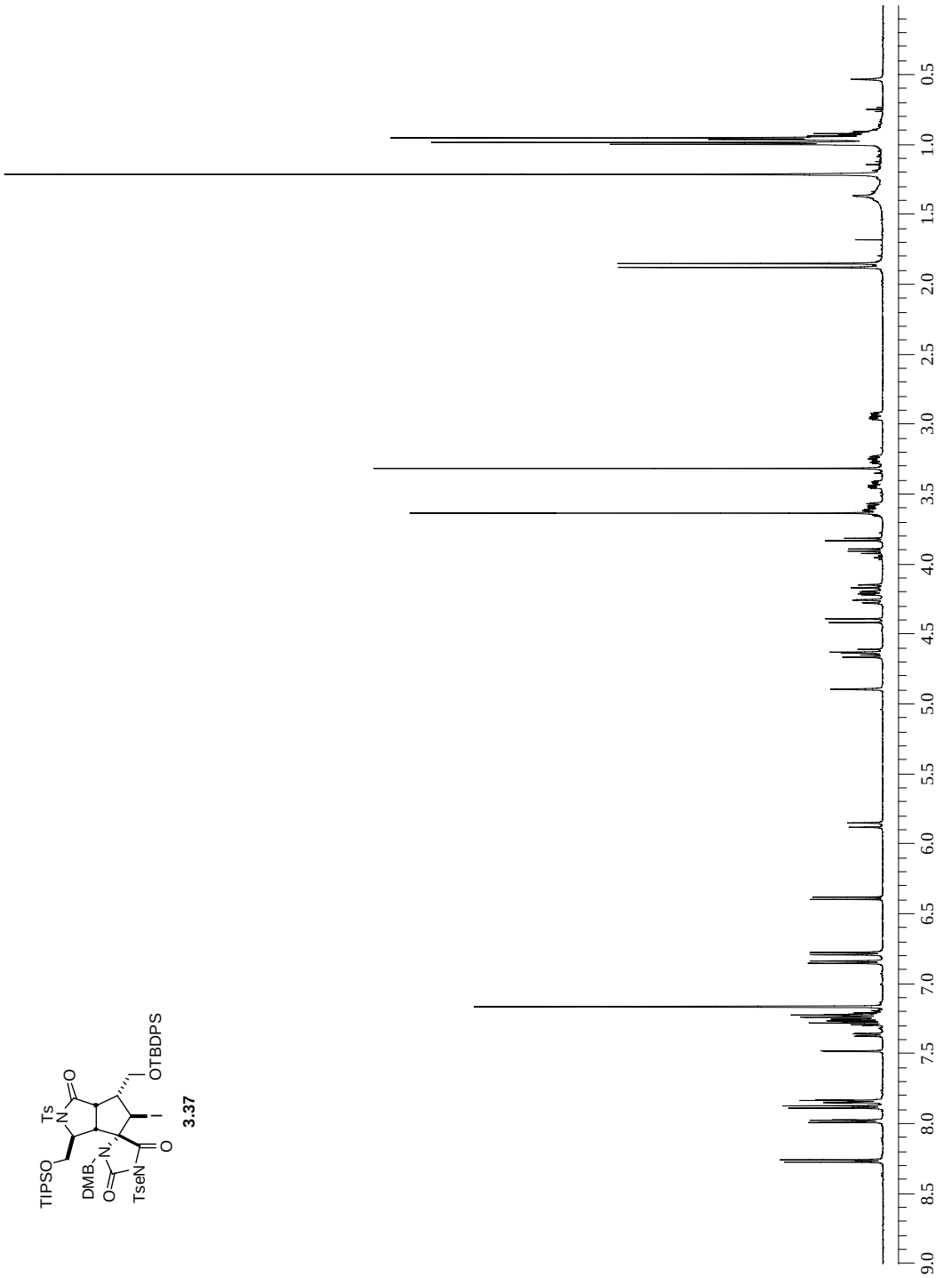
^{13}C-NMR spectrum of TBDPS silylether **3.27** (in benzene-d_6)



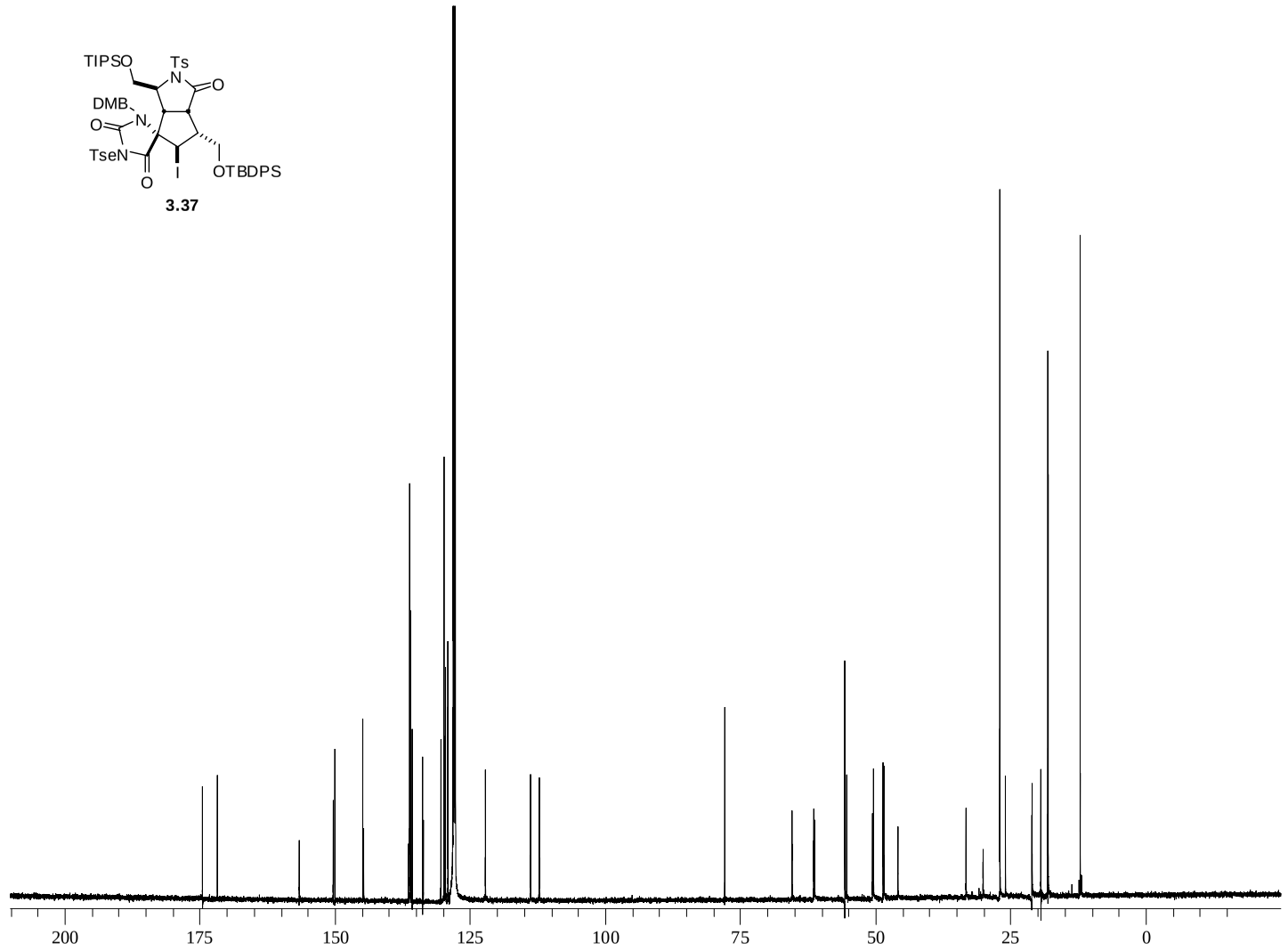
^{1}H-NMR spectrum of allylic alcohol **3.28** (in benzene-d_6)



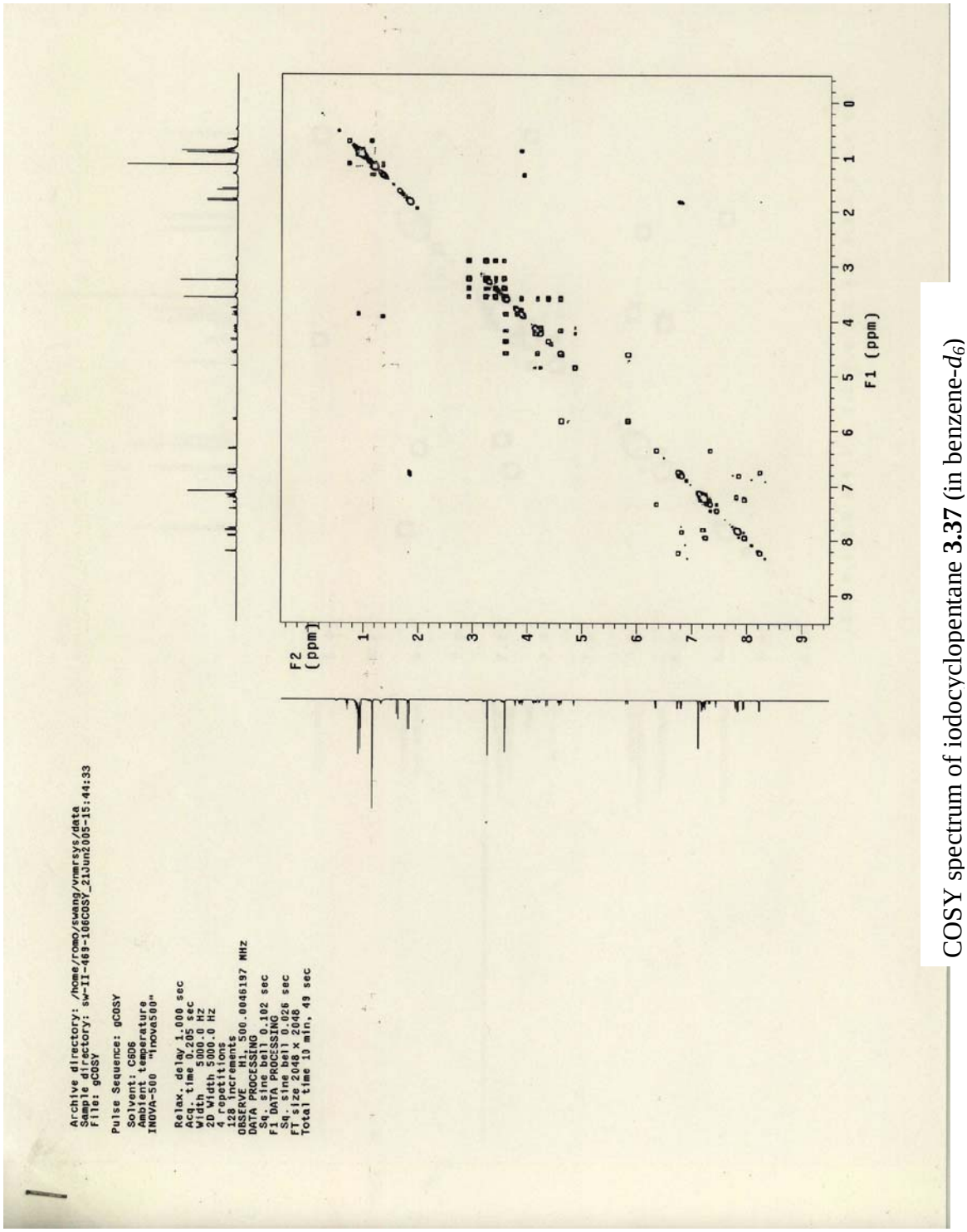
^{13}C-NMR spectrum of allylic alcohol **3.28** (in benzene-d_6)



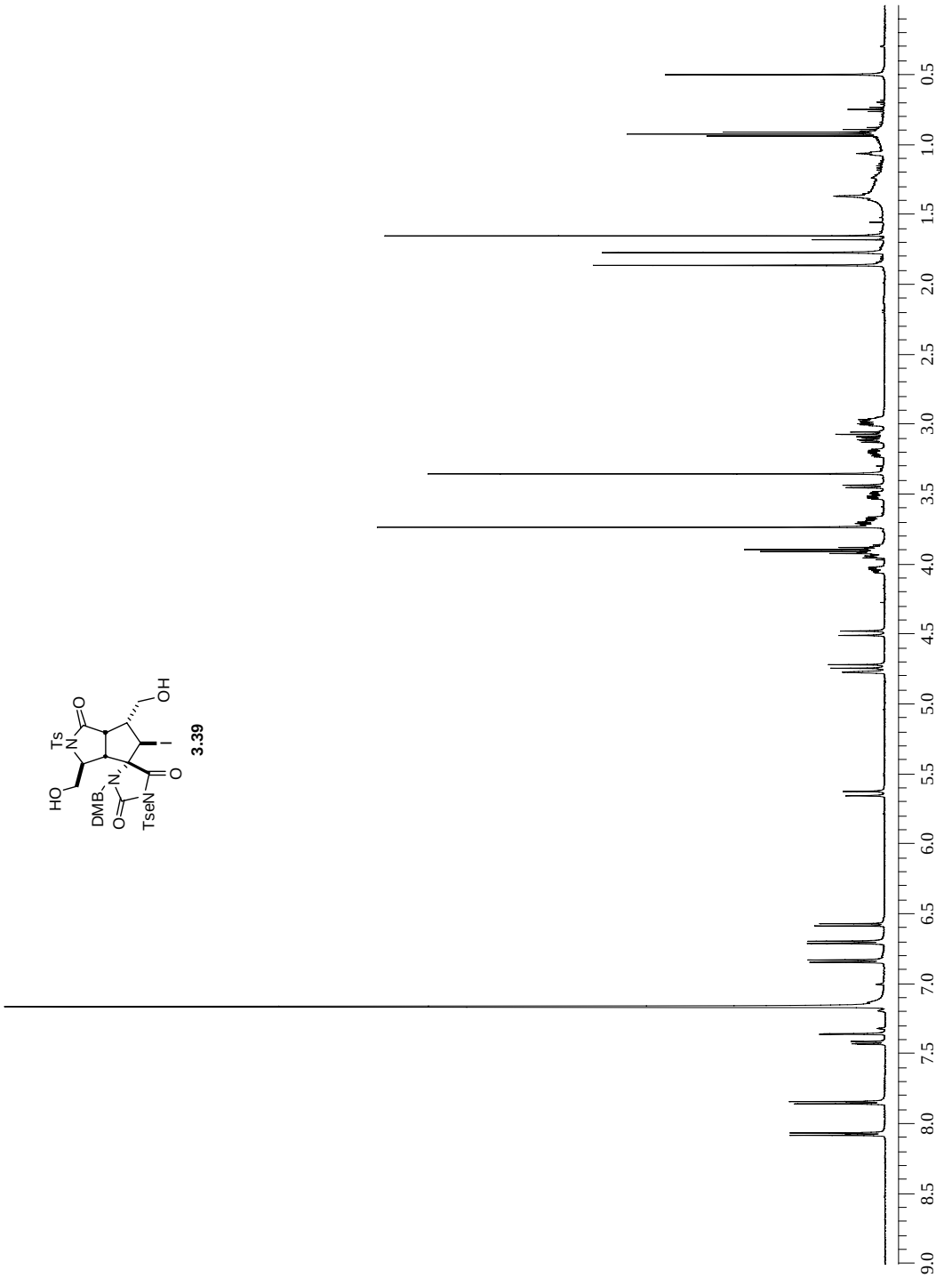
^{1}H-NMR spectrum of iodocyclopentane **3.37** (in benzene-d_6)



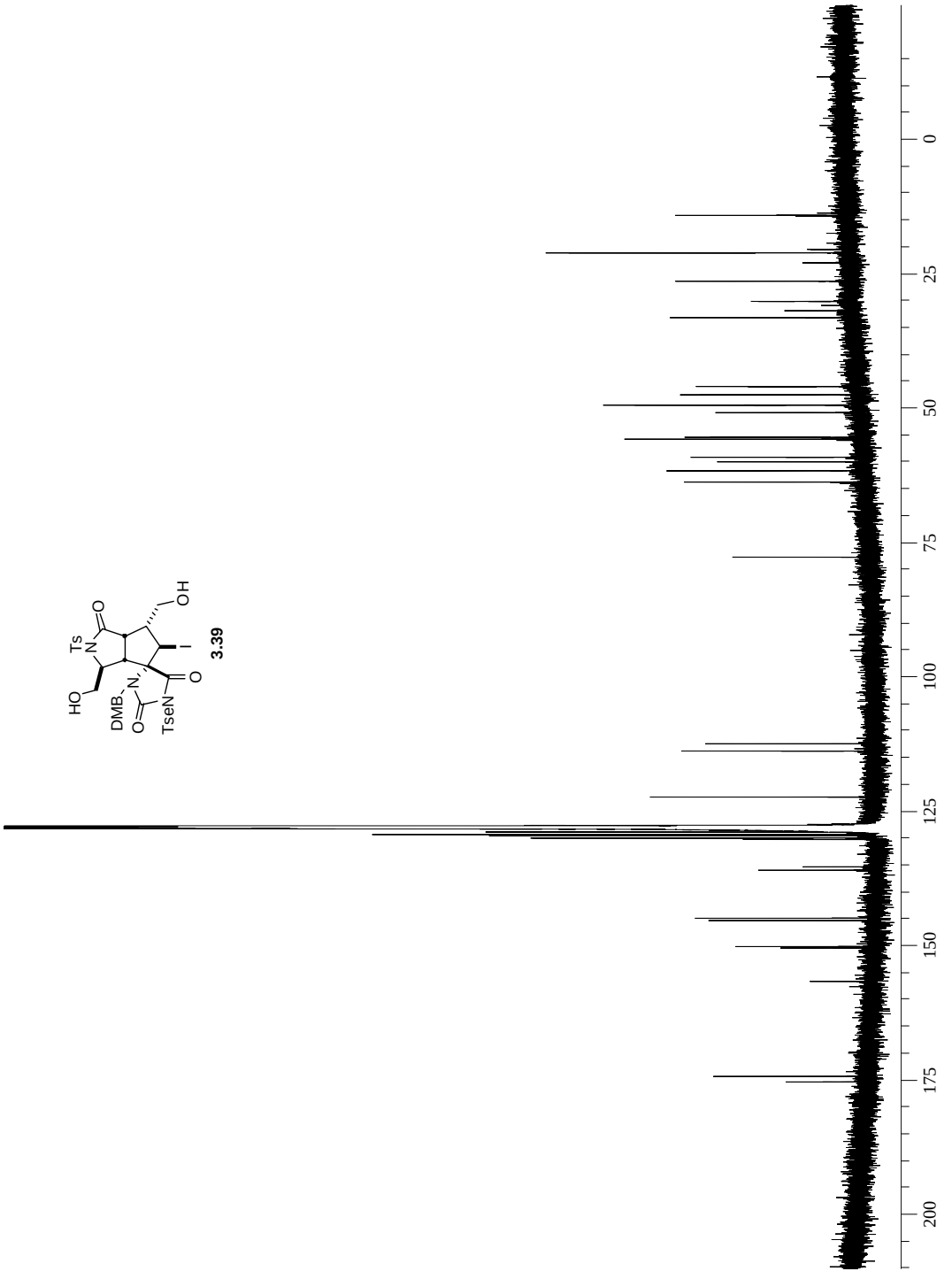
^{13}C-NMR spectrum of iodocyclopentane **3.37** (in benzene-d_6)



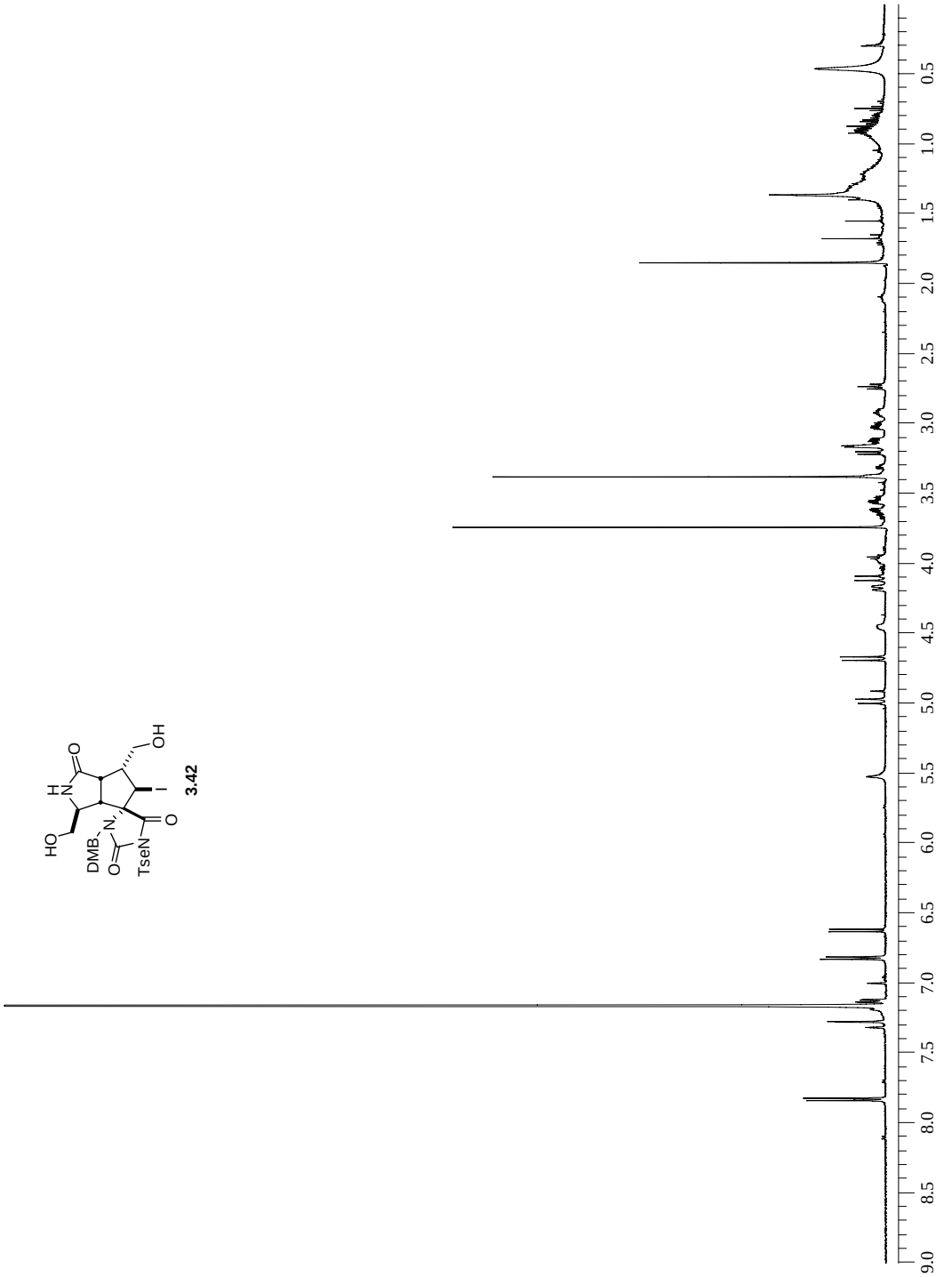
COSY spectrum of iodocyclopentane **3.37** (in benzene-d_6)



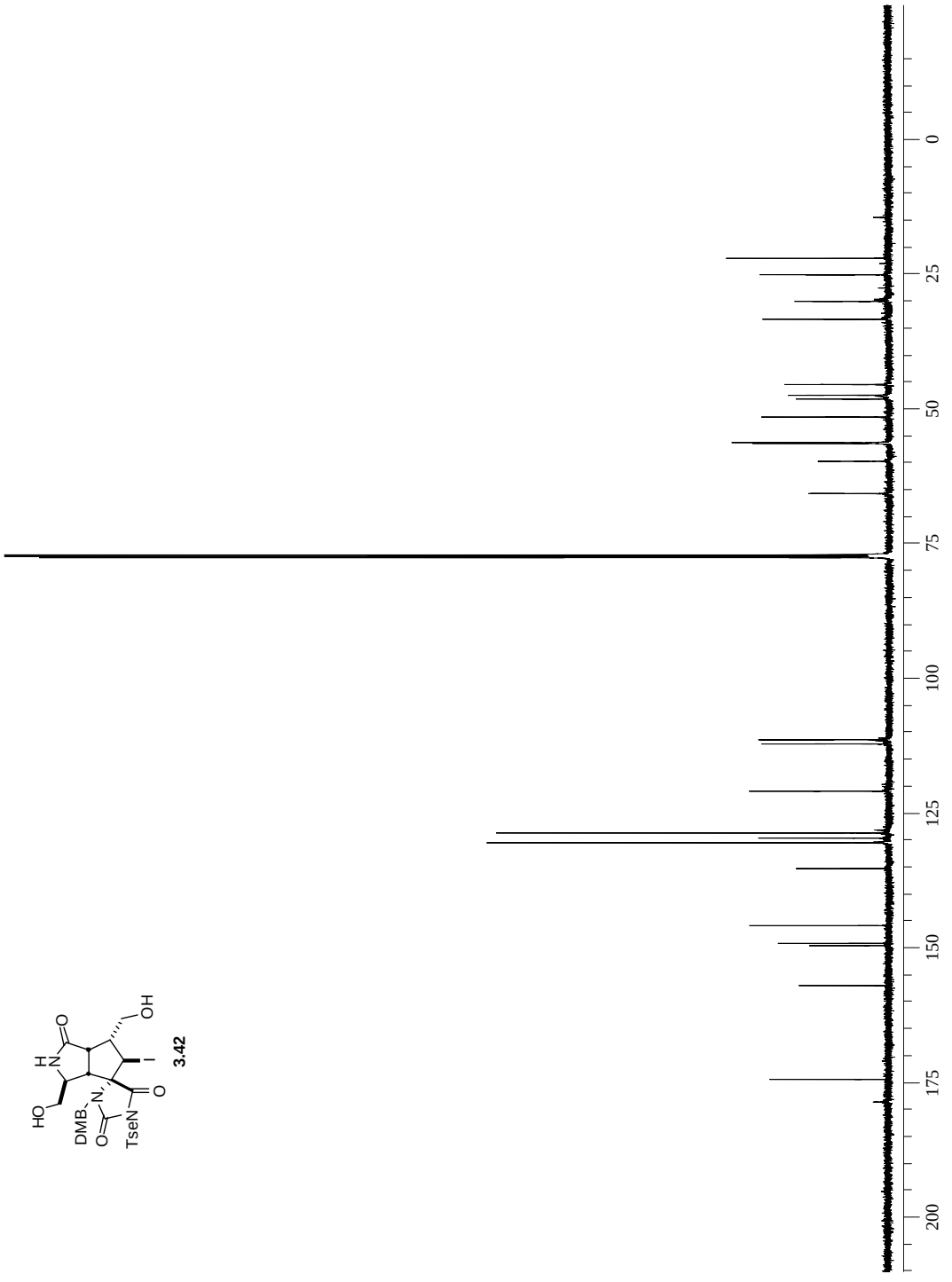
^{1}H-NMR spectrum of diol **3.39** (in benzene-d_6)



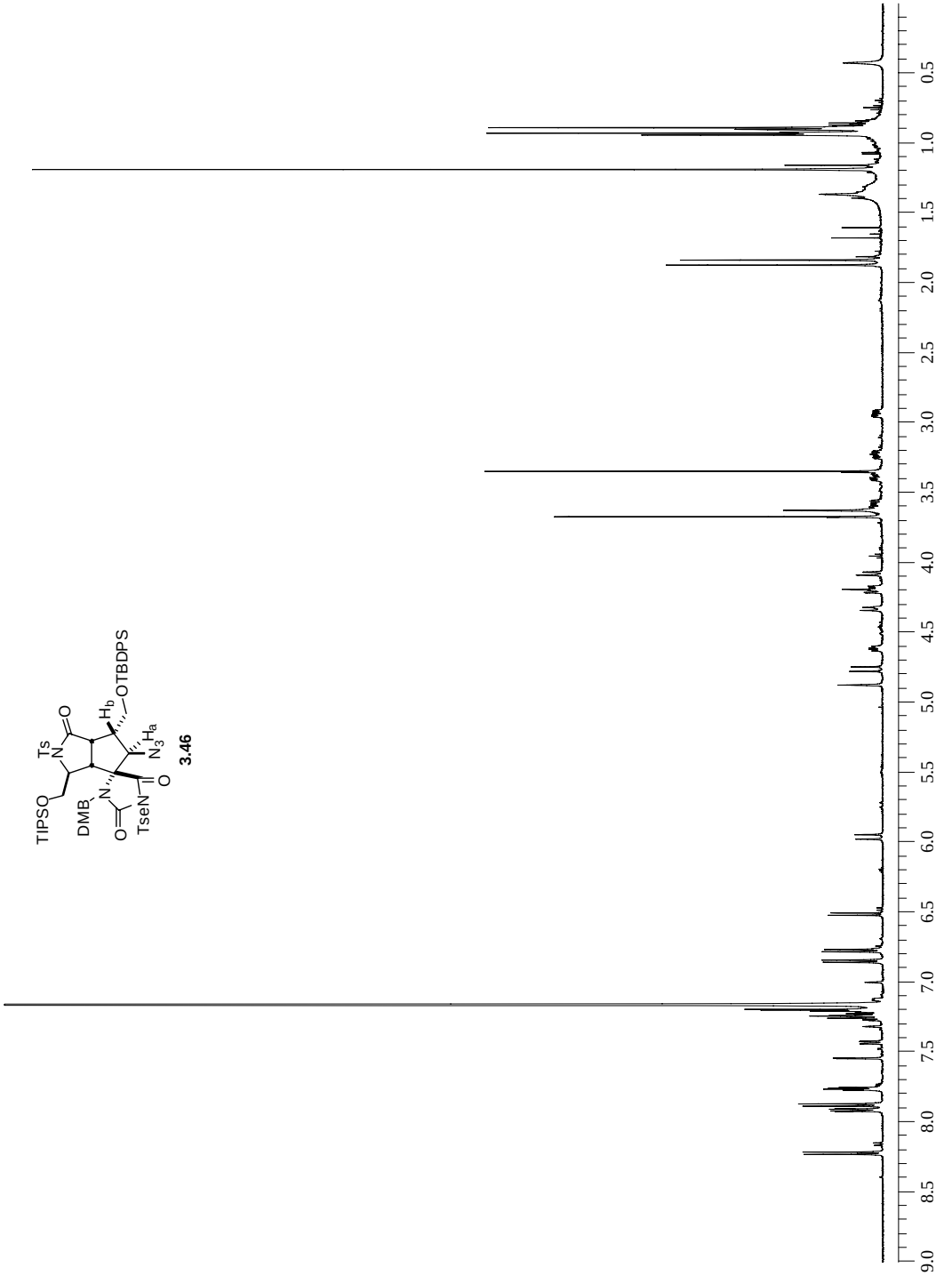
^{13}C-NMR spectrum of diol **3.39** (in benzene-d_6)



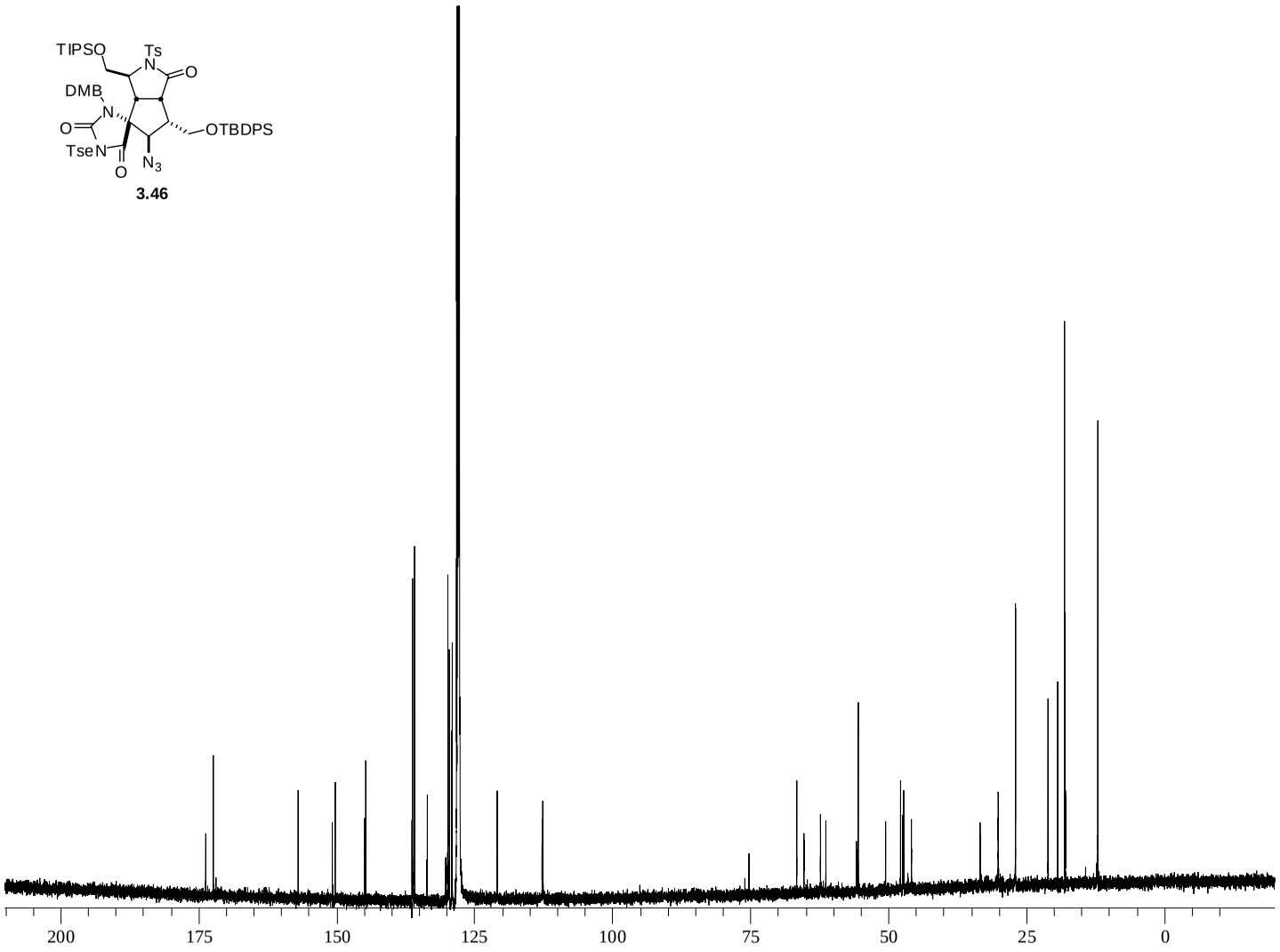
^{1}H-NMR spectrum of lactam **3.42** (in benzene-d_6)



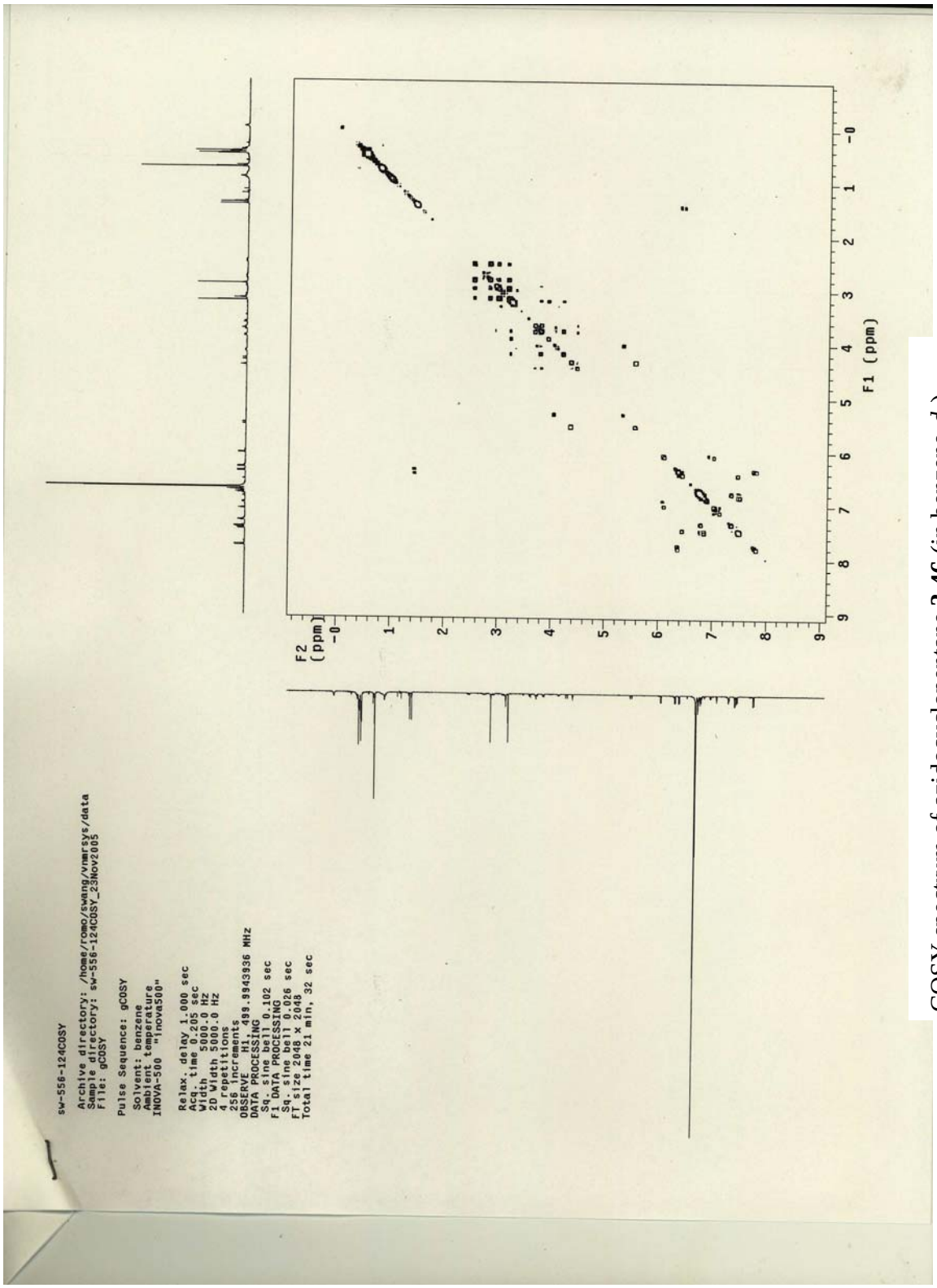
^{13}C-NMR spectrum of lactam **3.42** (in benzene-d_6)



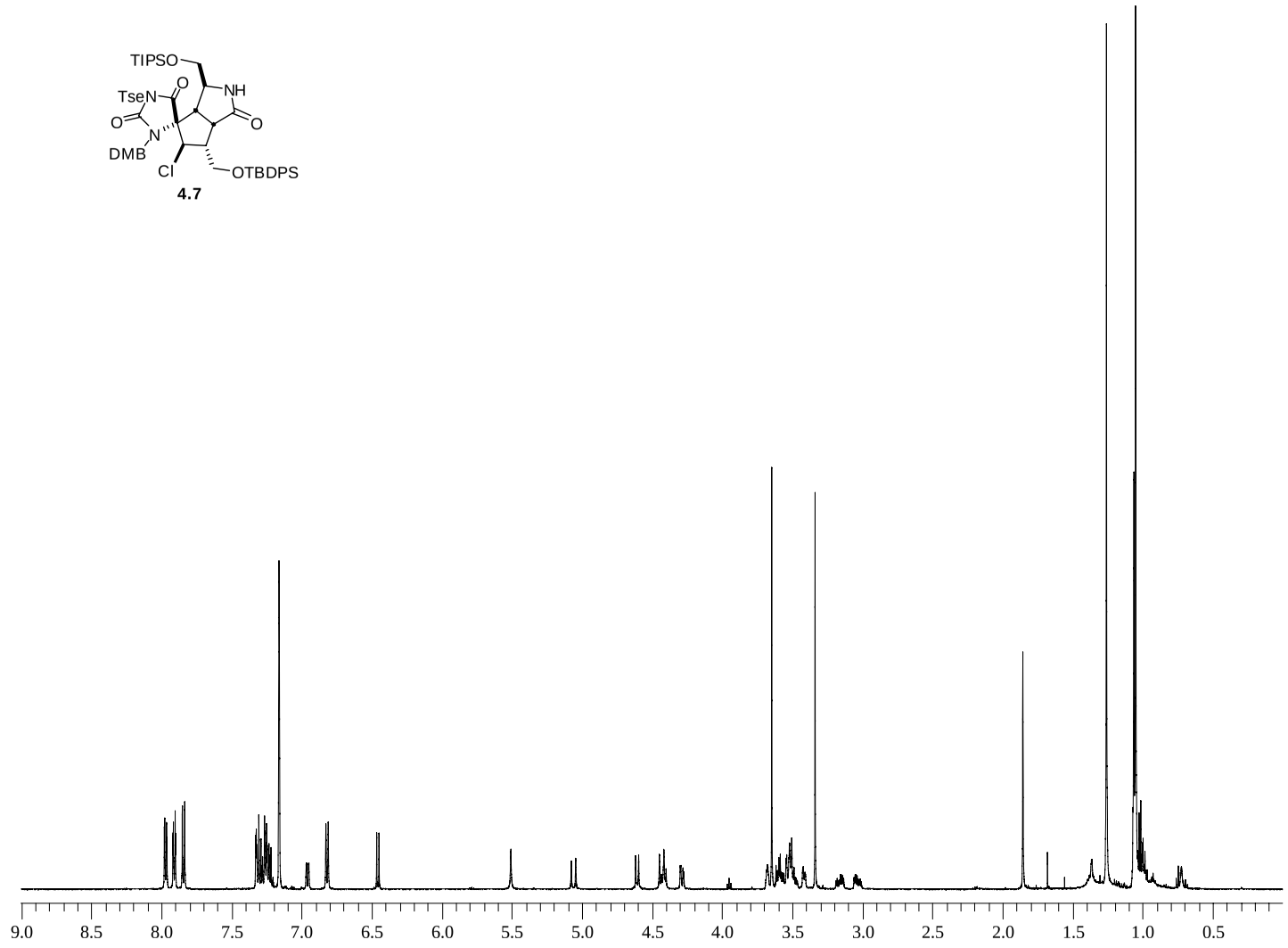
^{1}H-NMR spectrum of azidocyclopentane **3.46** (in benzene-d_6)



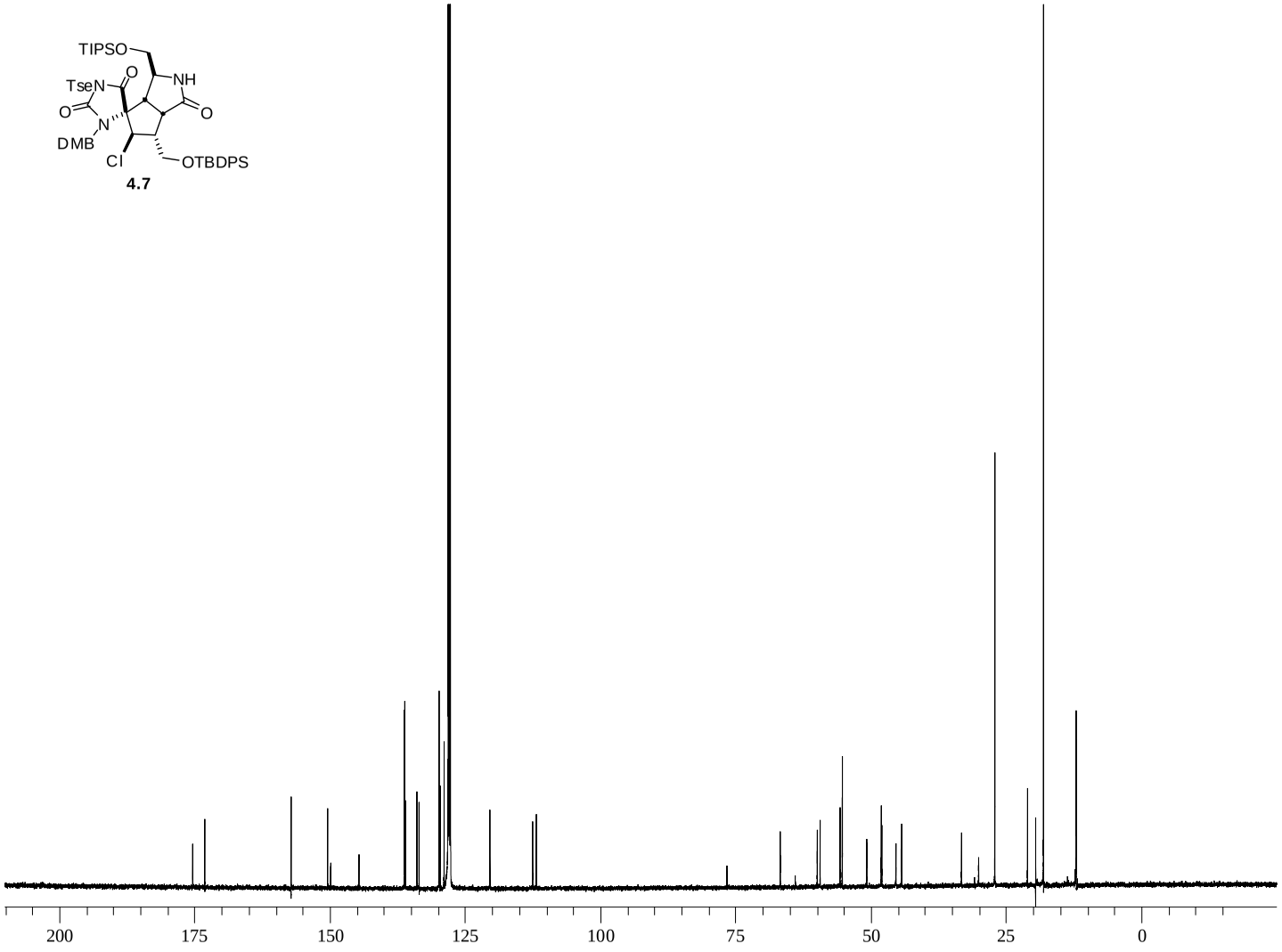
^{13}C-NMR spectrum of azidocyclopentane **3.46** (in benzene-d_6)



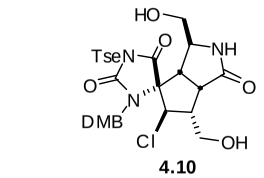
COSY spectrum of azidocyclopentane **3.46** (in benzene-d_6)



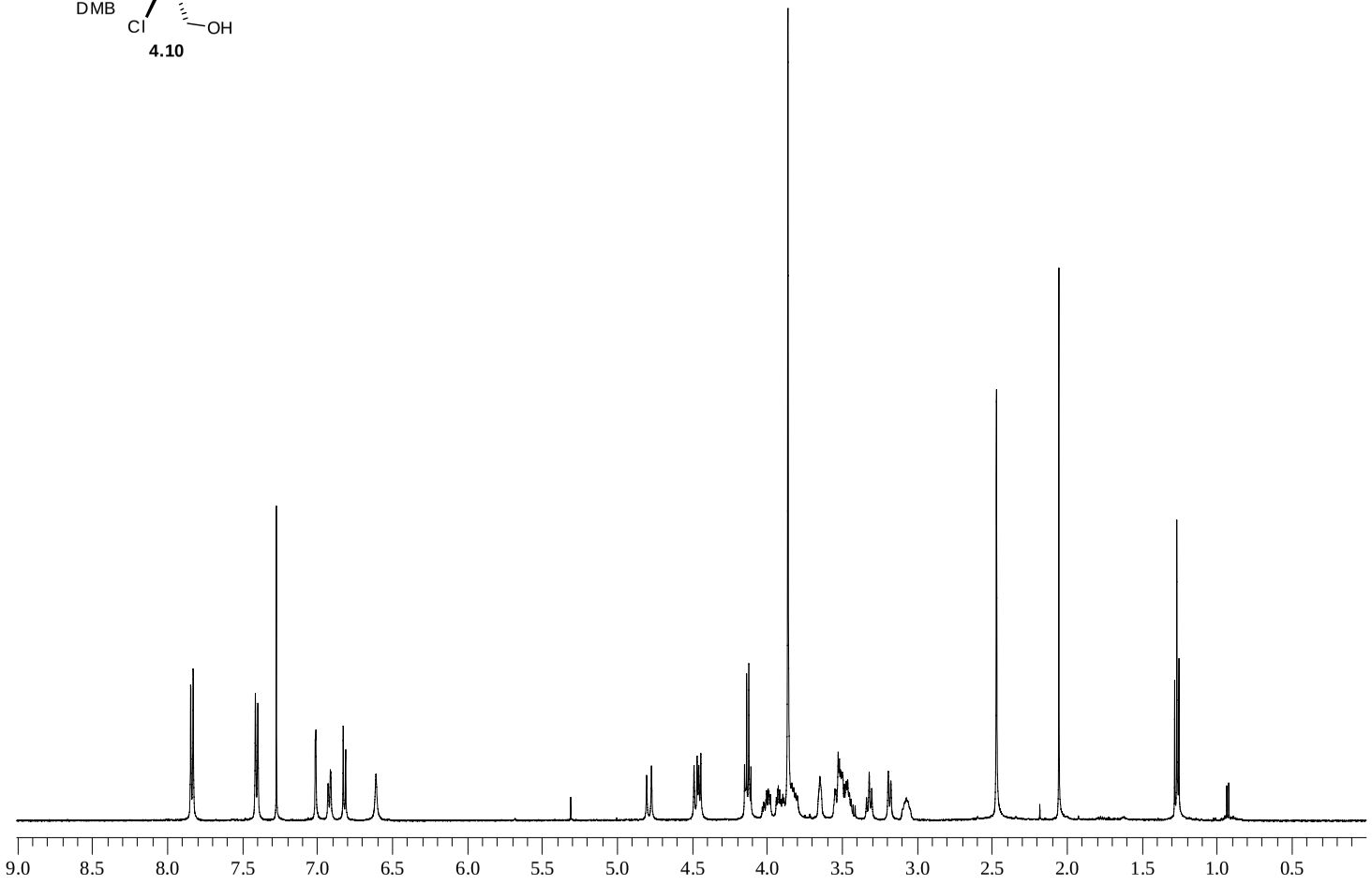
^{1}H-NMR spectrum of lactam **4.7** (in benzene-d_6)



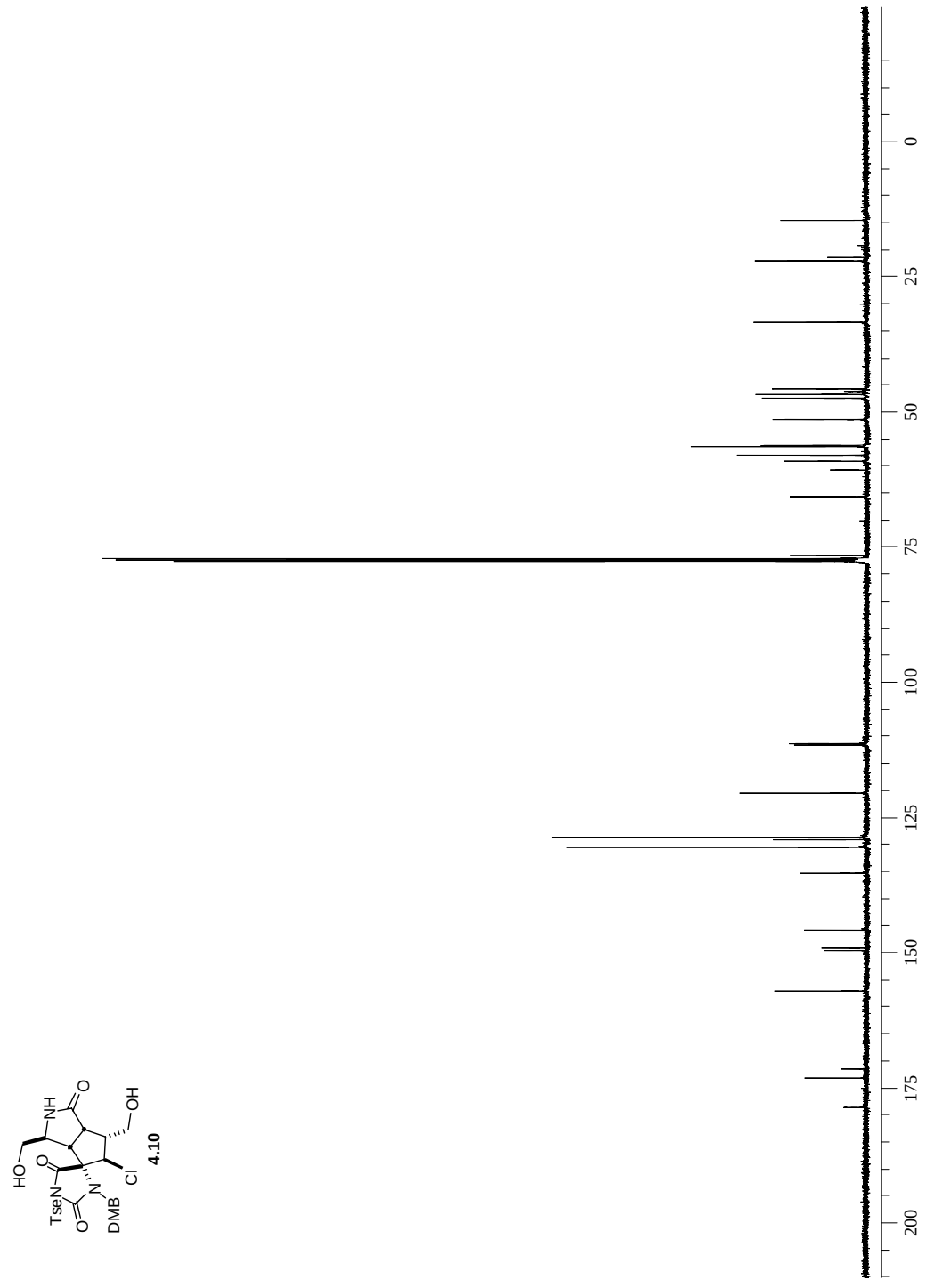
^{13}C-NMR spectrum of lactam **4.7** (in benzene-d_6)



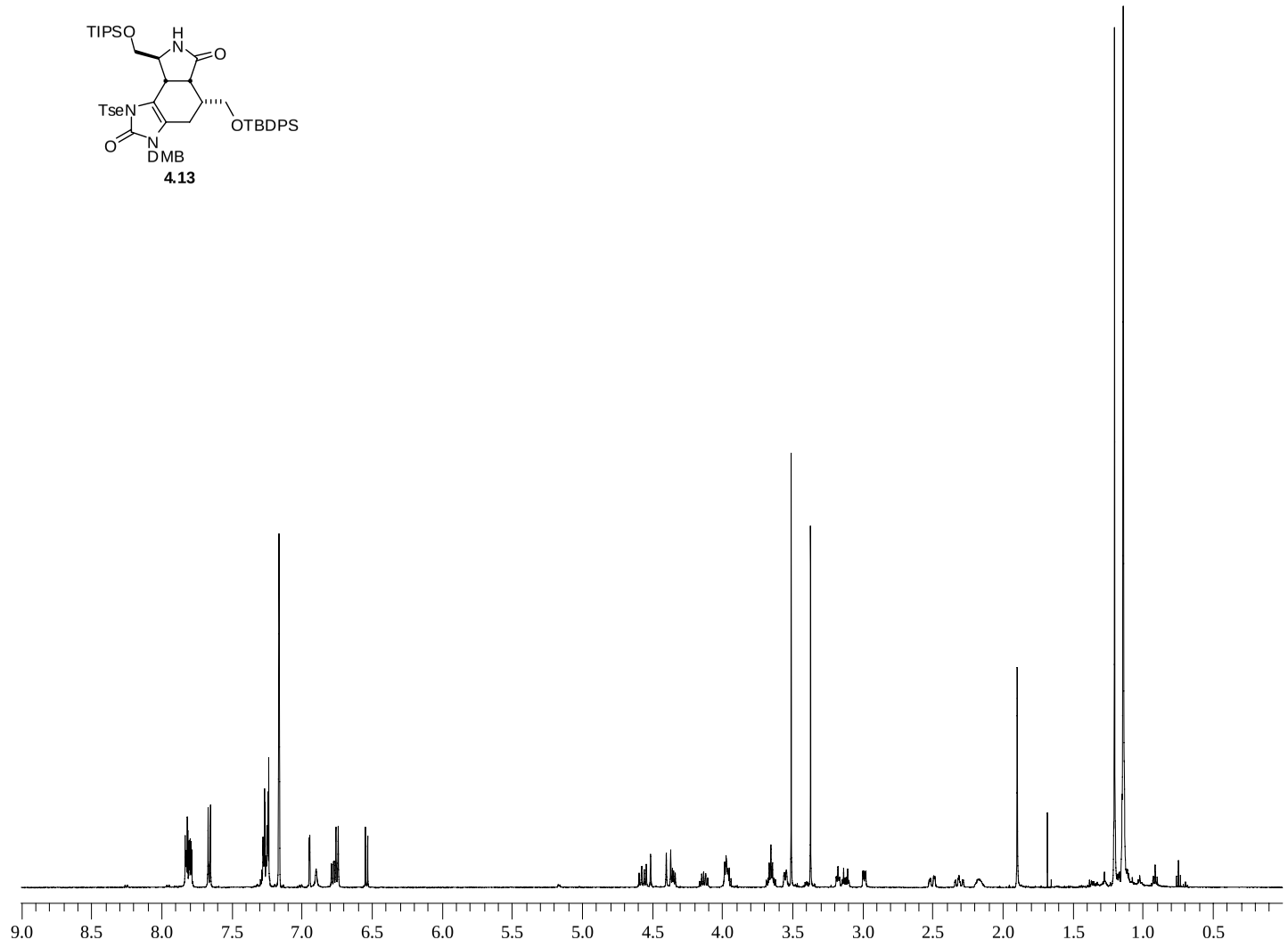
4.10



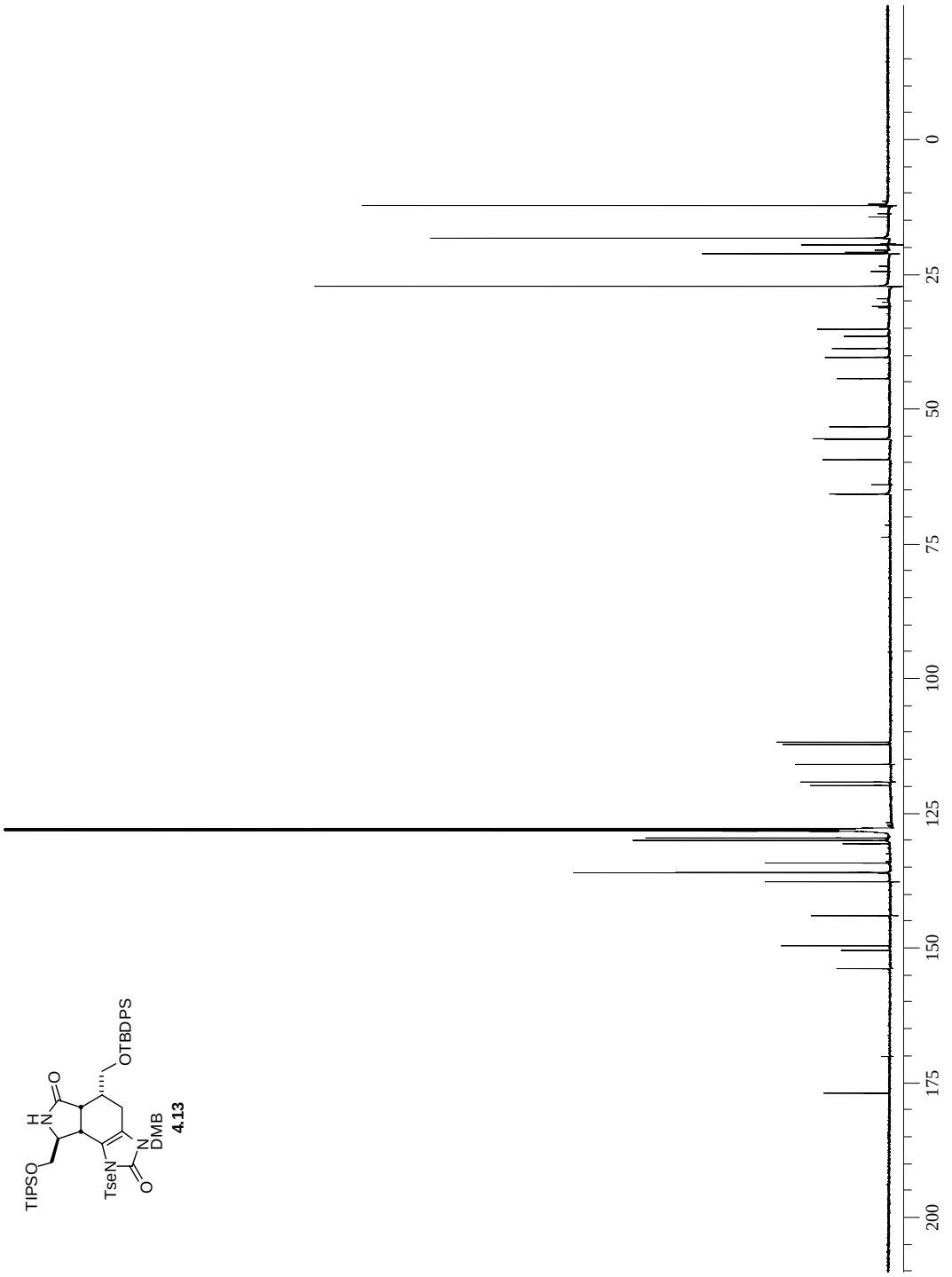
^{1}H-NMR spectrum of diol **4.10** (in $CDCl_3$)



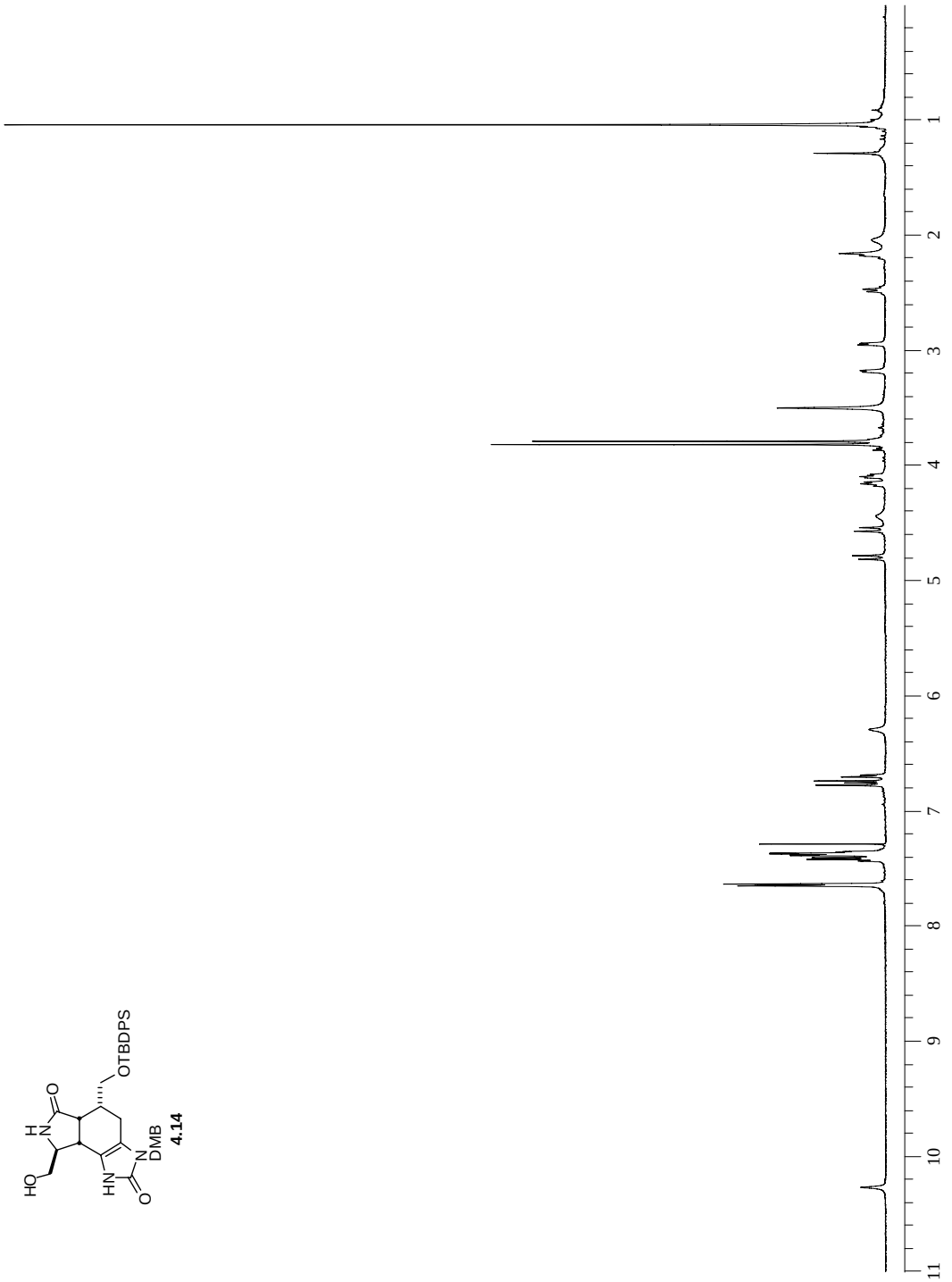
^{13}C-NMR spectrum of diol **4.10** (in $CDCl_3$)



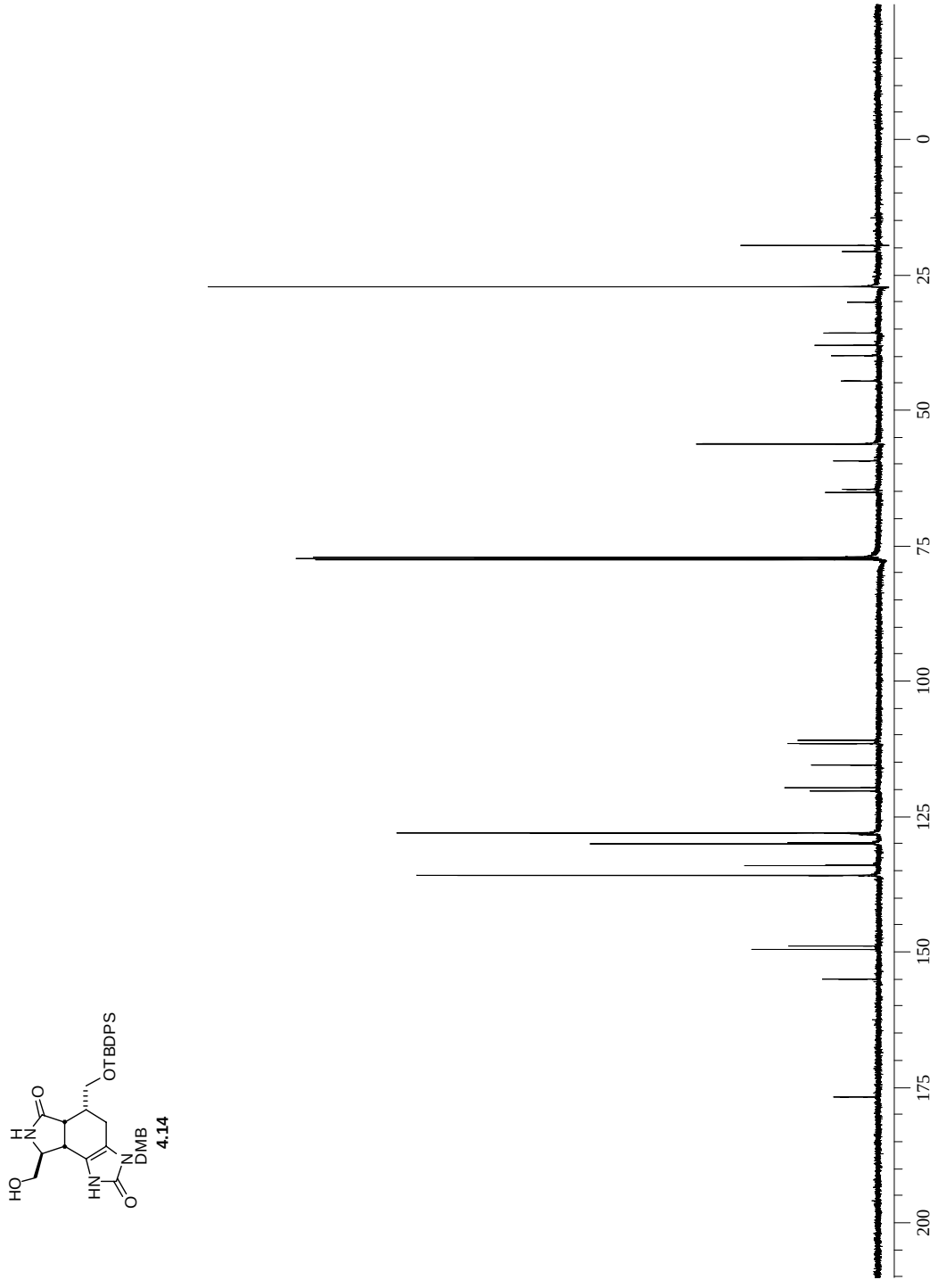
^{1}H-NMR spectrum of lactam **4.13** (in benzene-d_6)



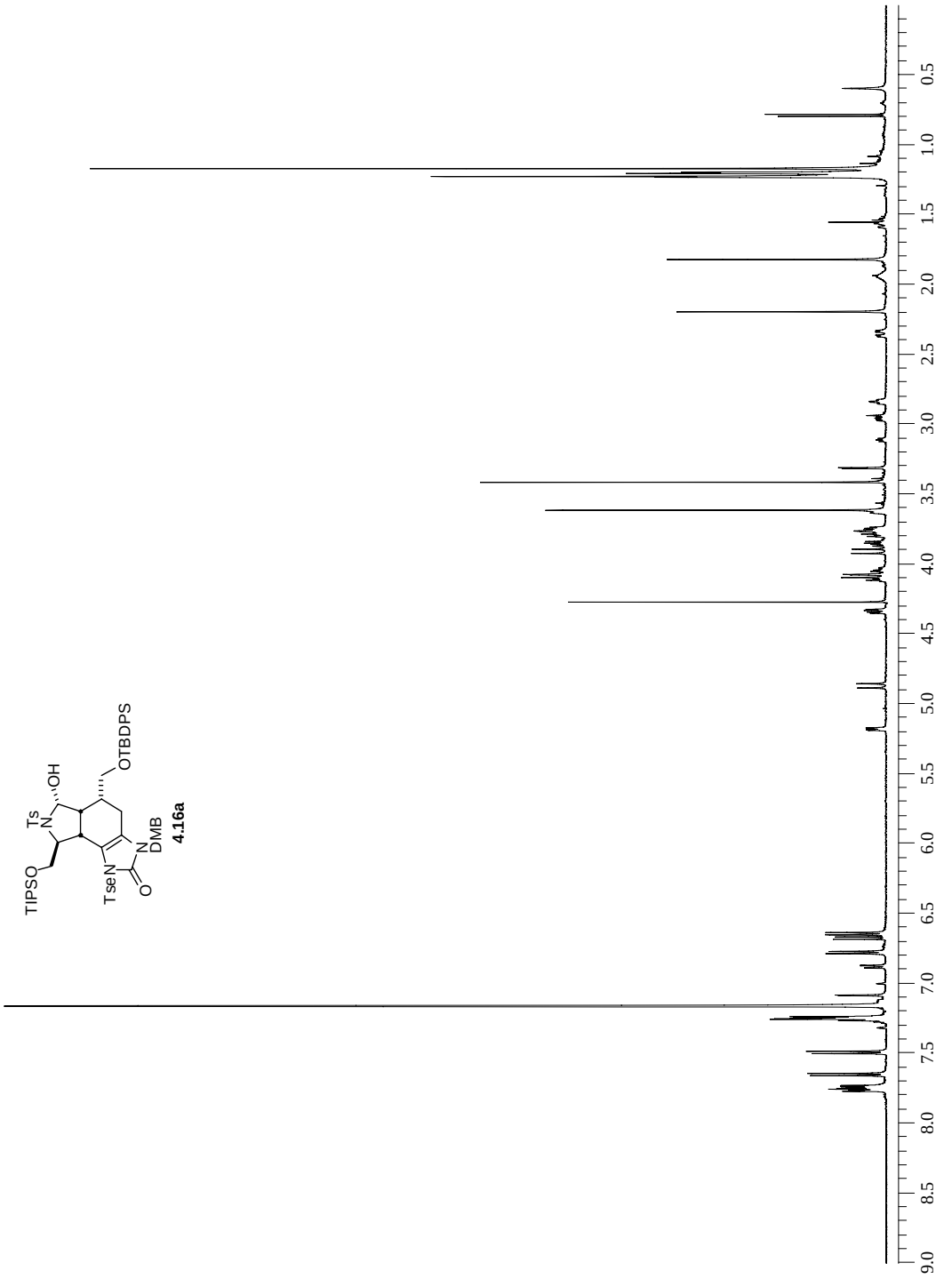
^{13}C-NMR spectrum of lactam **4.13** (in benzene-d_6)



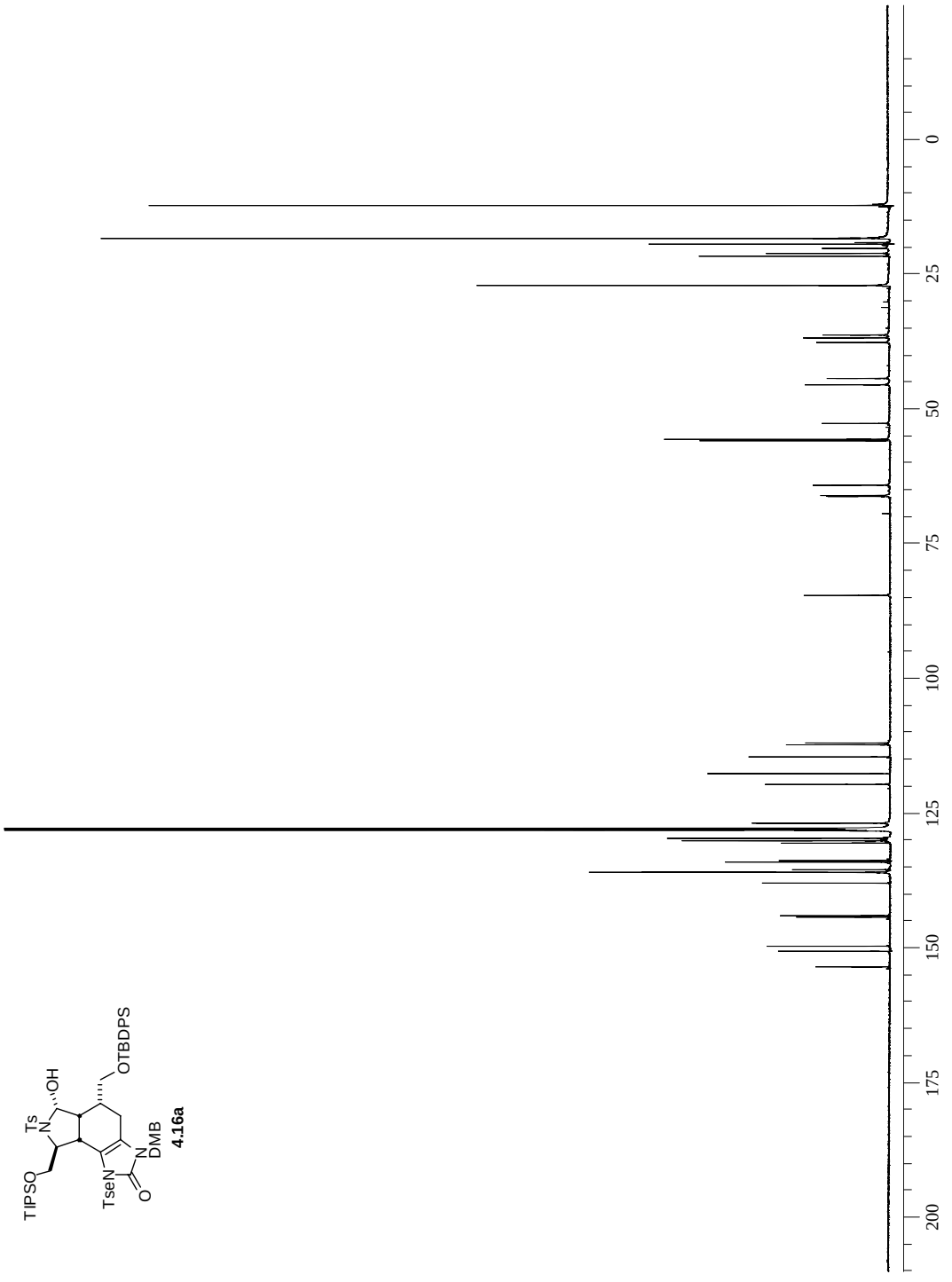
^{1}H-NMR spectrum of alcohol **4.14** (in $CDCl_3$)



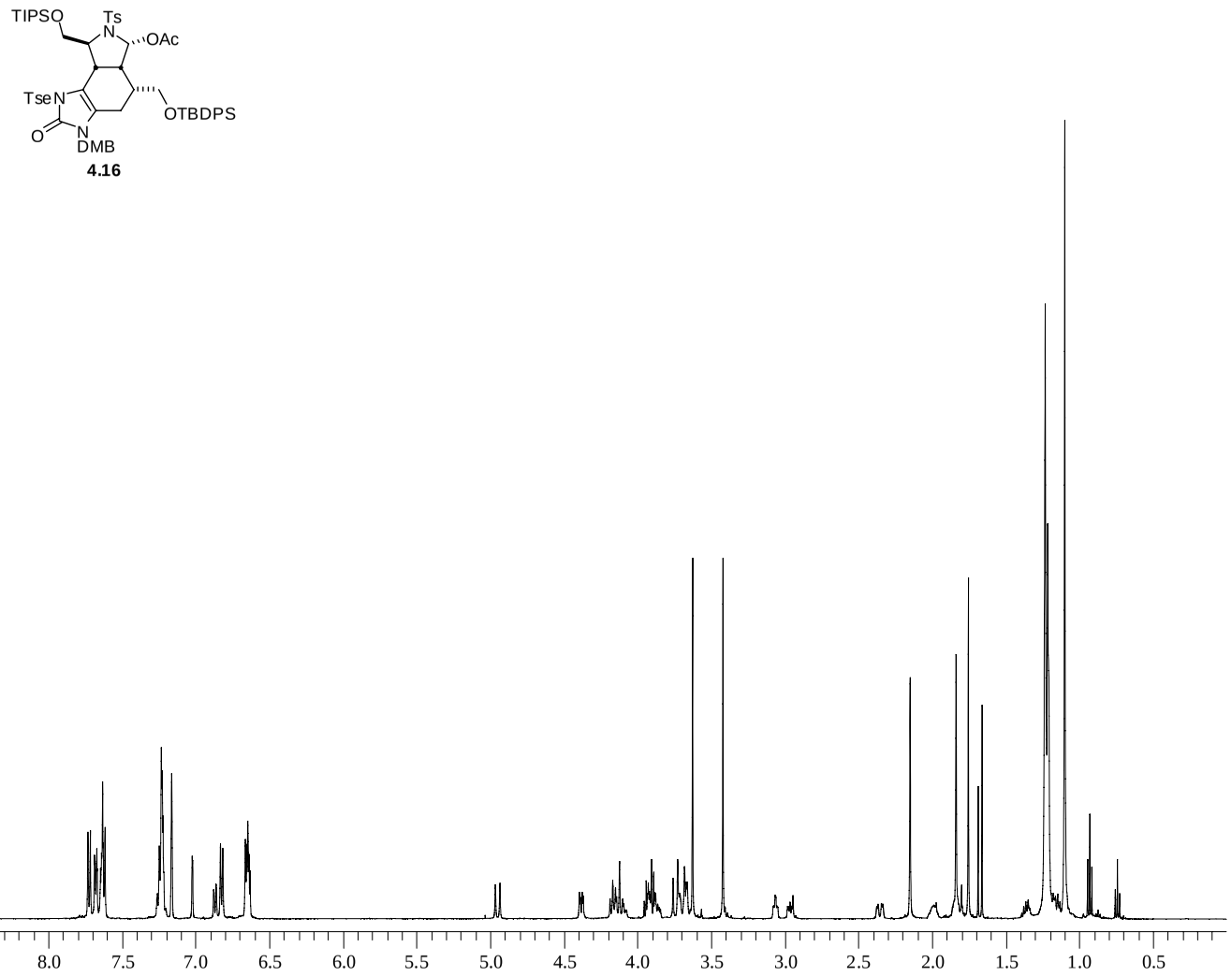
^{13}C-NMR spectrum of alcohol **4.14** (in $CDCl_3$)



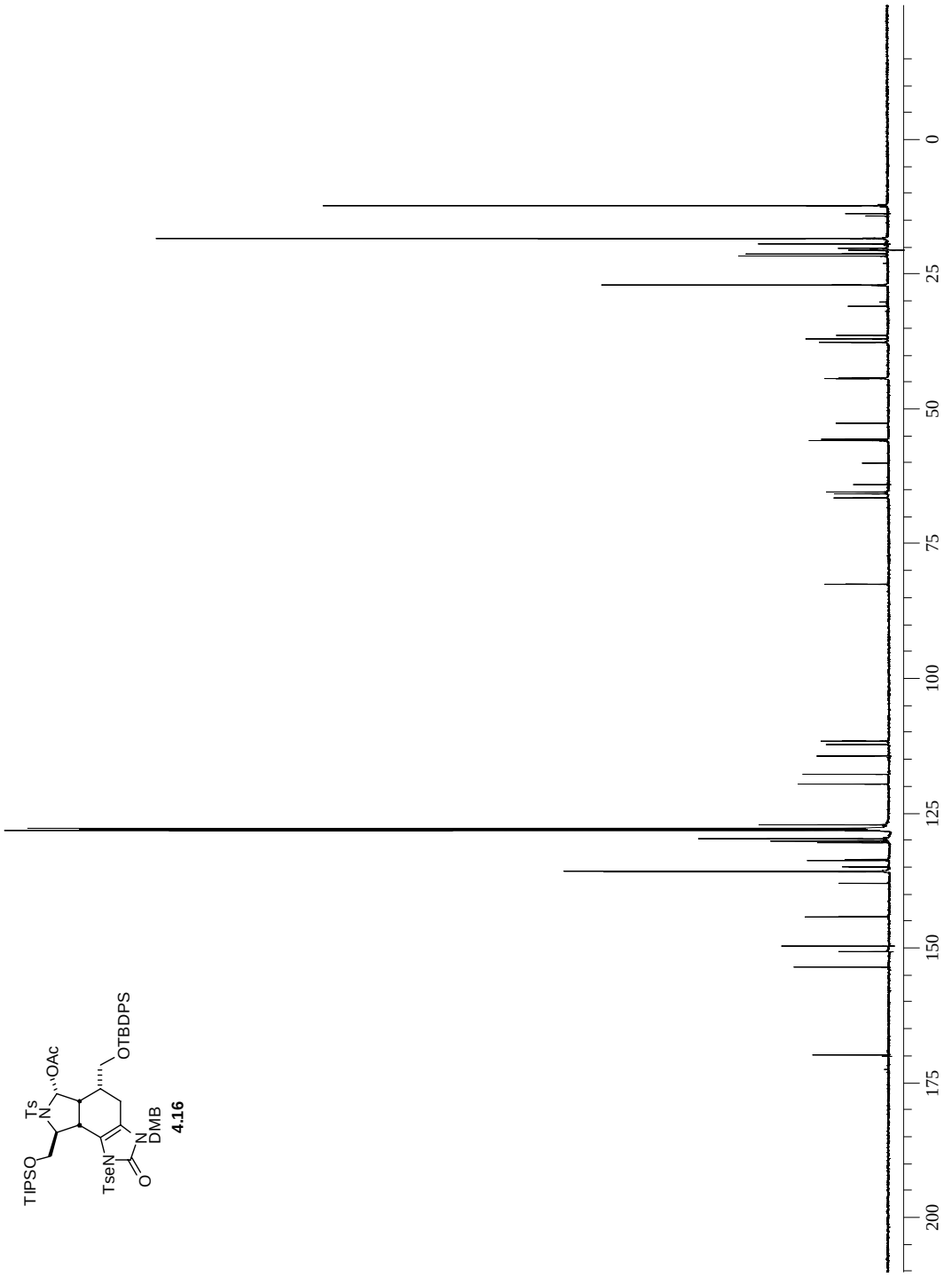
^{1}H-NMR spectrum of aminal **4.16a** (in benzene-d_6)



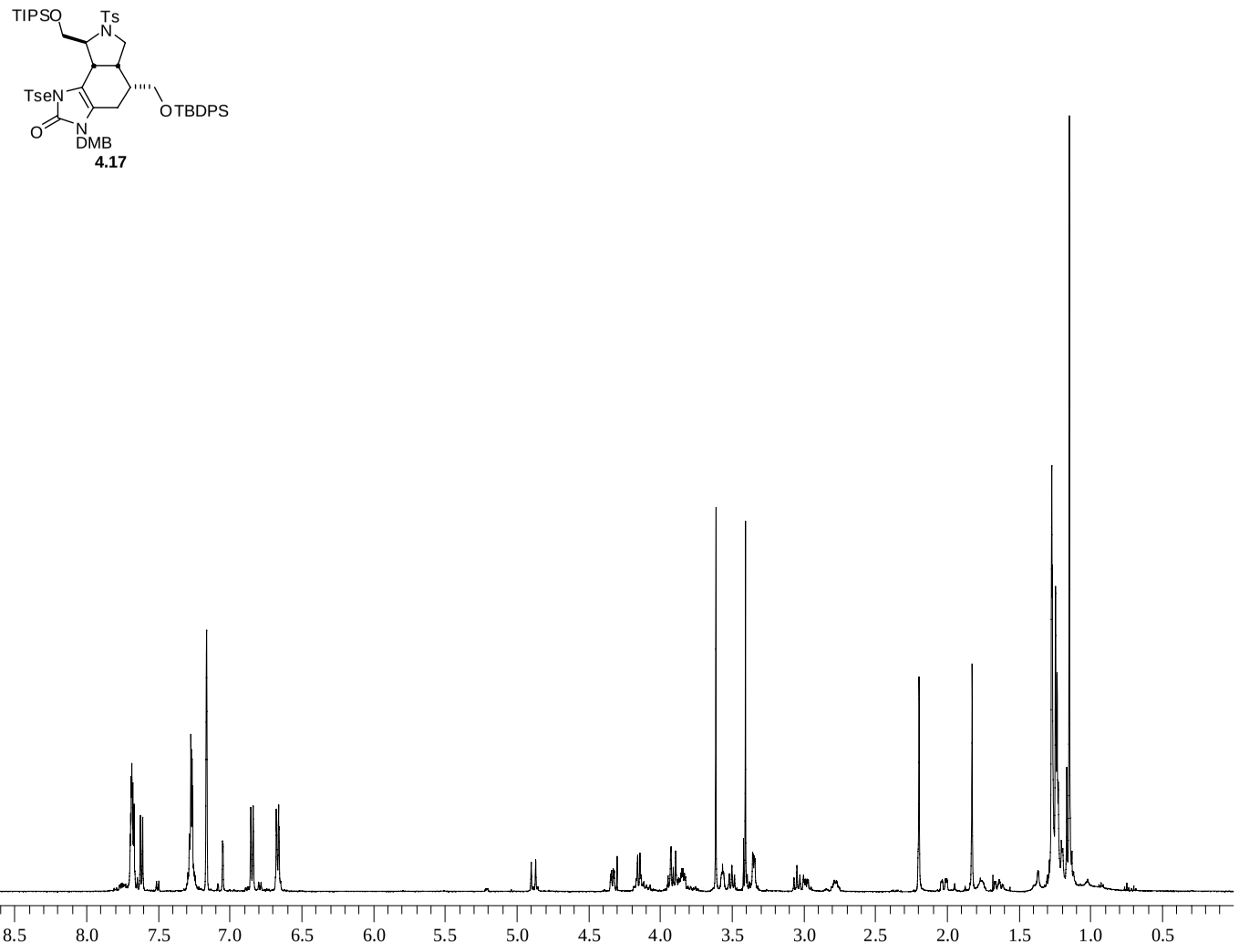
^{13}C-NMR spectrum of aminal **4.16a** (in benzene-d_6)



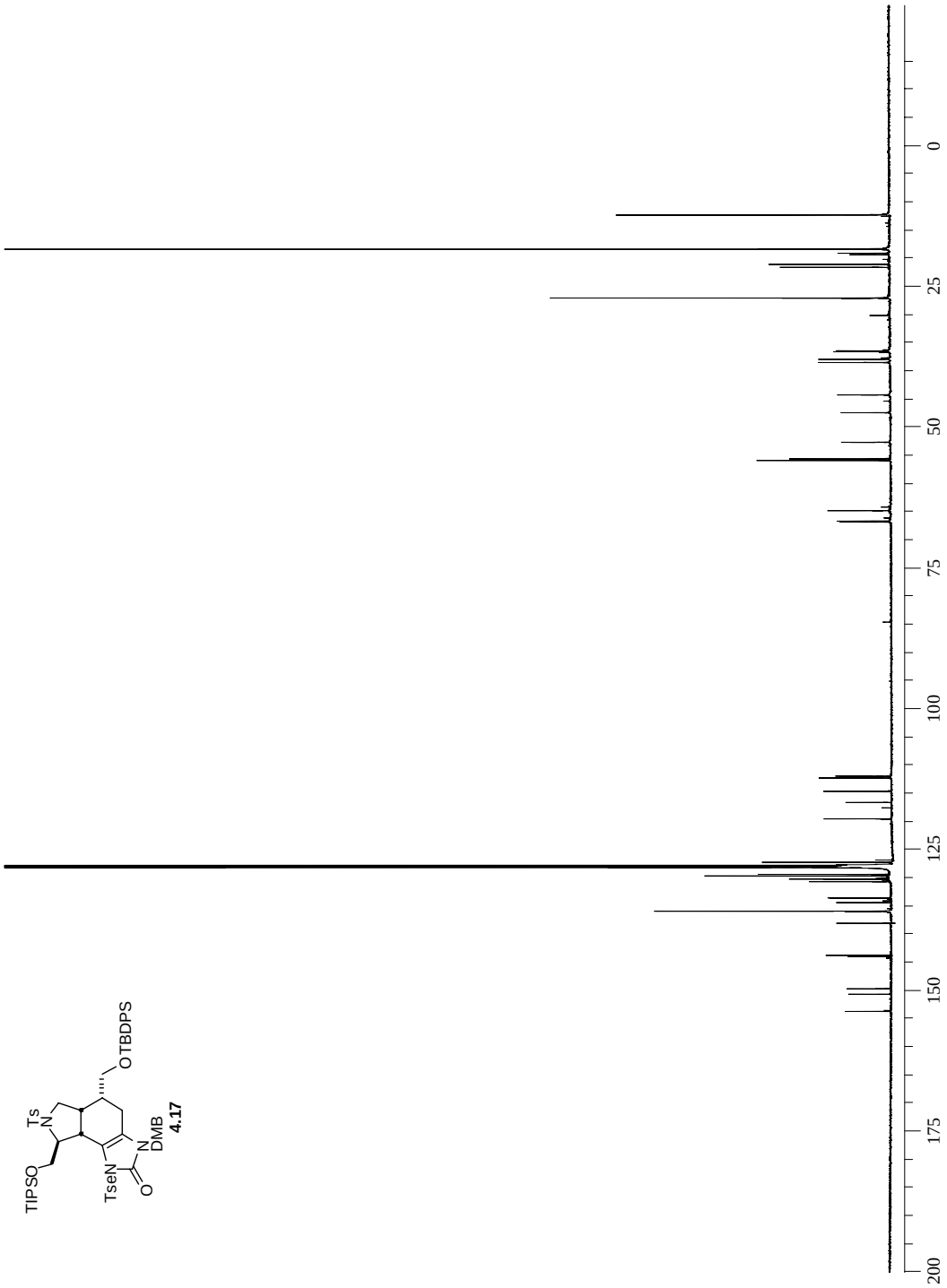
^{1}H-NMR spectrum of acetate **4.16** (in benzene-d_6)



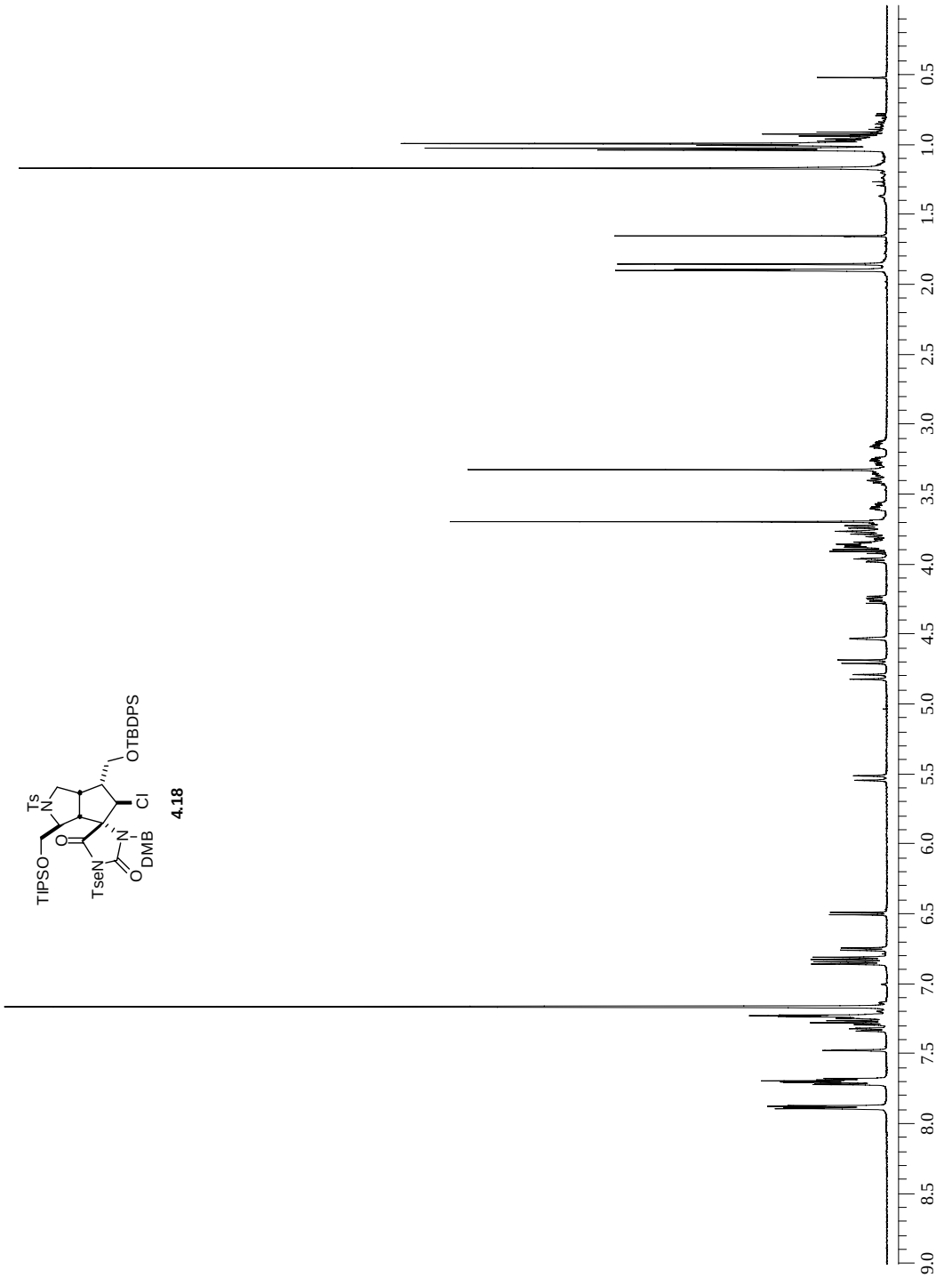
^{13}C-NMR spectrum of acetate **4.16** (in benzene-d_6)



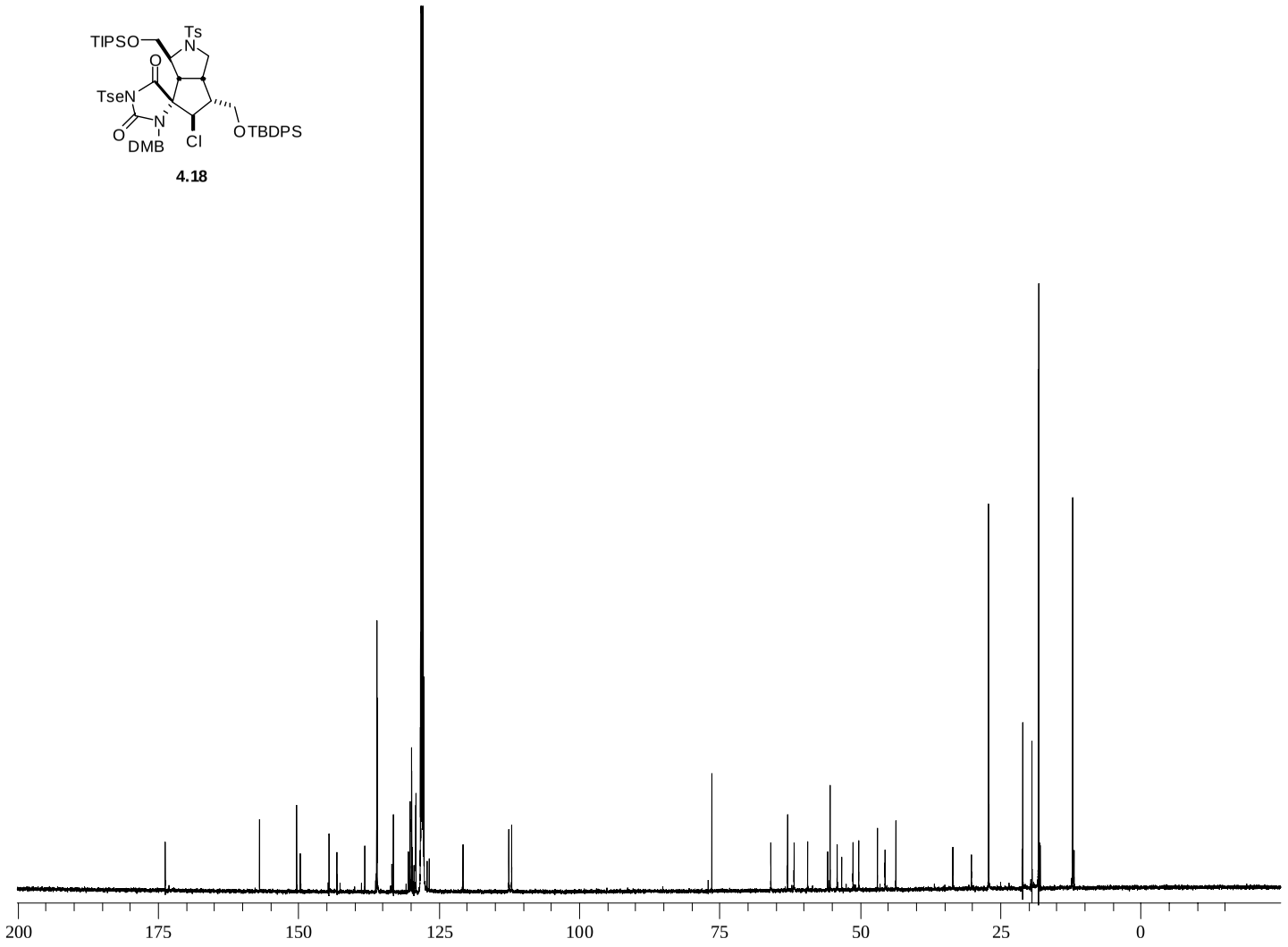
^{1}H-NMR spectrum of Ts-protected pyrrolidine **4.17** (in benzene-d_6)



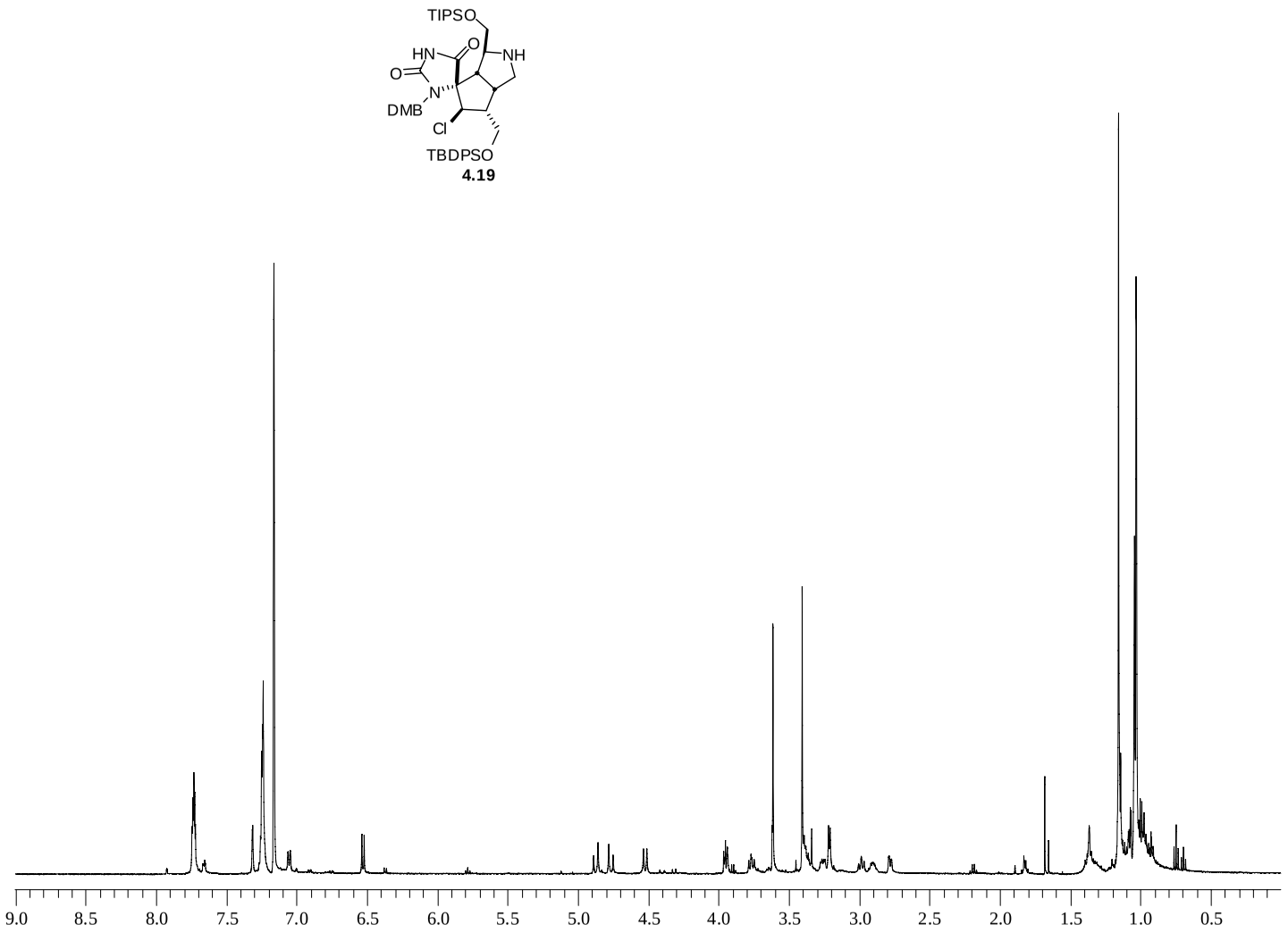
^{13}C-NMR spectrum of Ts-protected pyrrolidine **4.17** (in benzene-d_6)



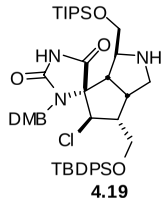
^{1}H-NMR spectrum of chlorocyclopentane **4.18** (in benzene-d_6)



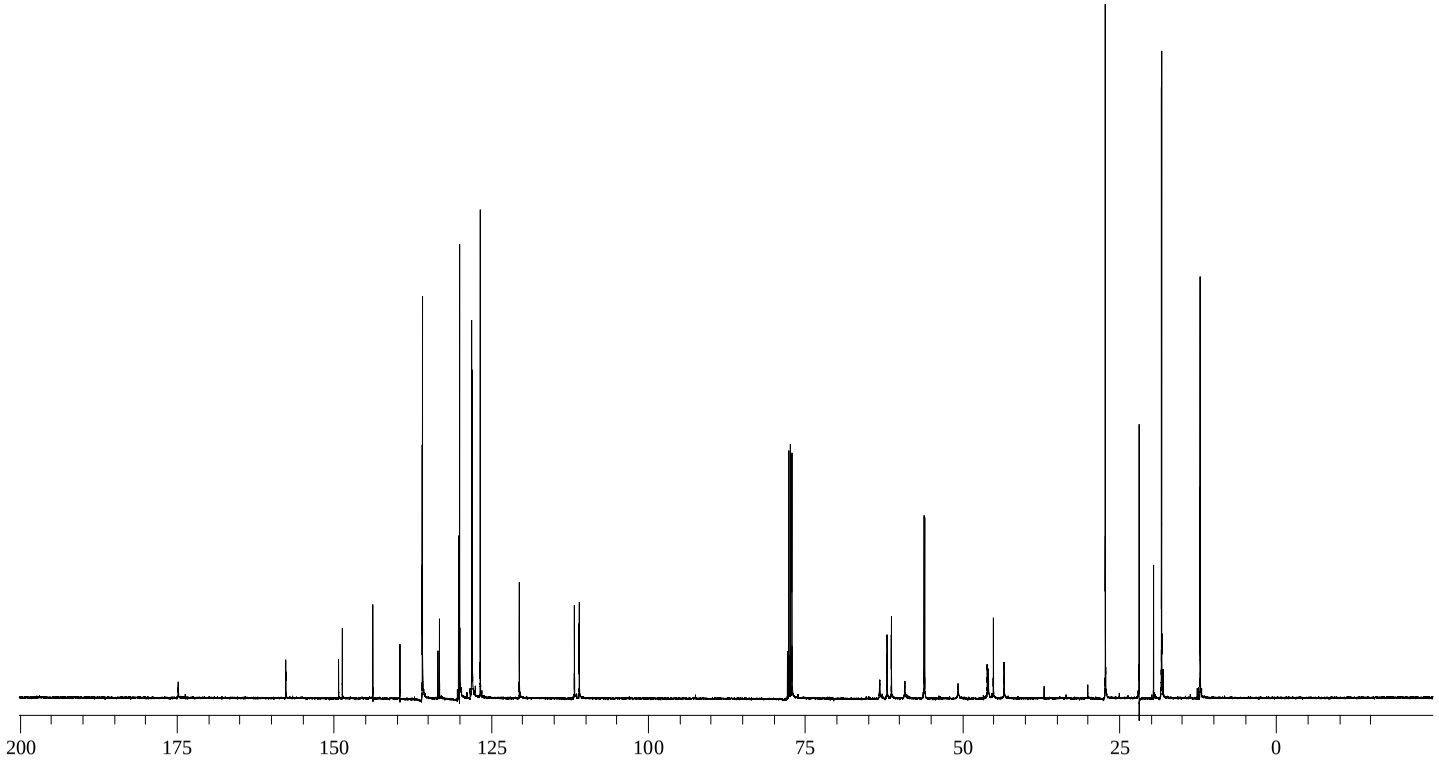
^{13}C-NMR spectrum of chlorocyclopentane **4.18** (in benzene-d_6)



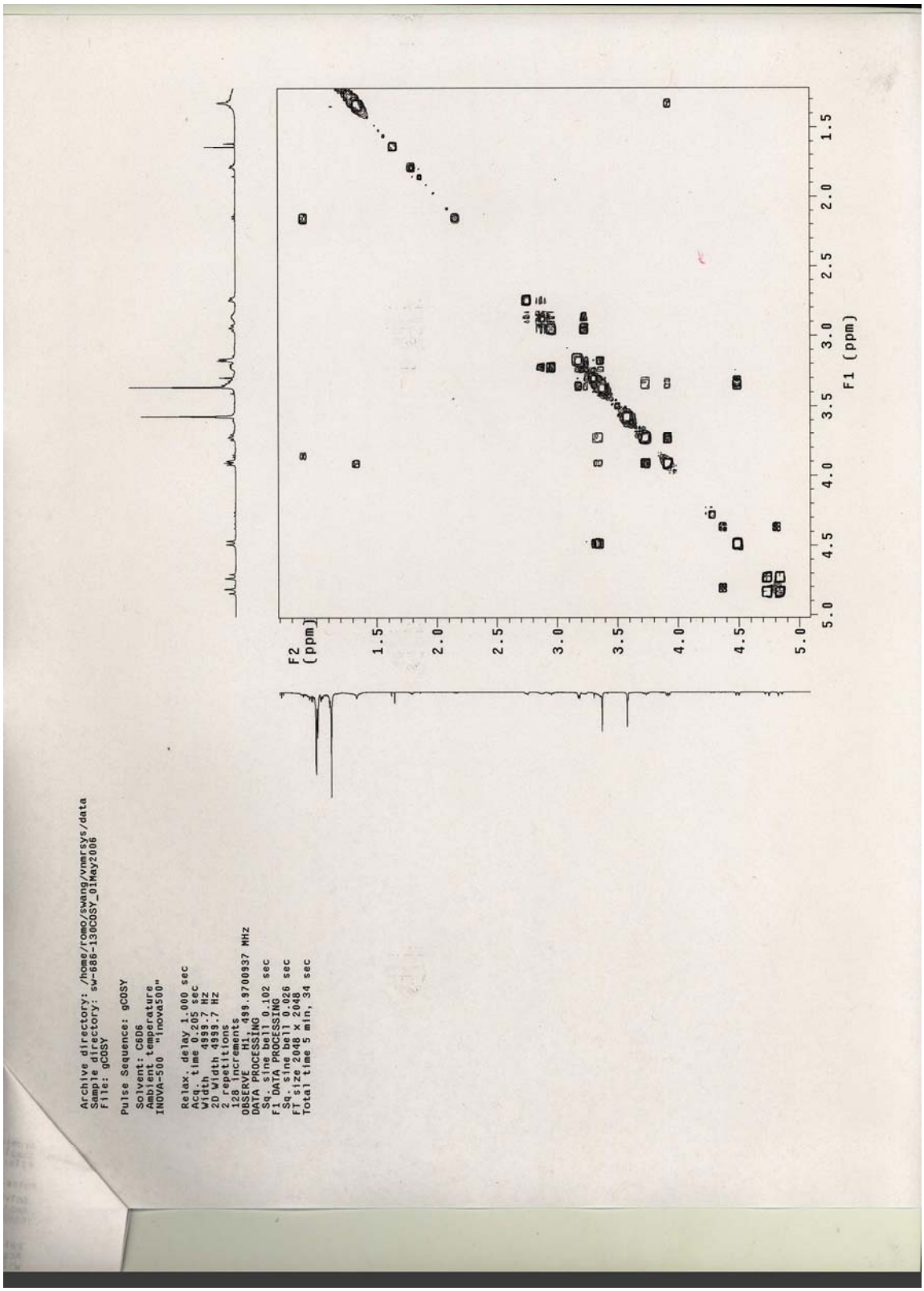
^{1}H-NMR spectrum of pyrrolidine **4.19** (in $CDCl_3$)



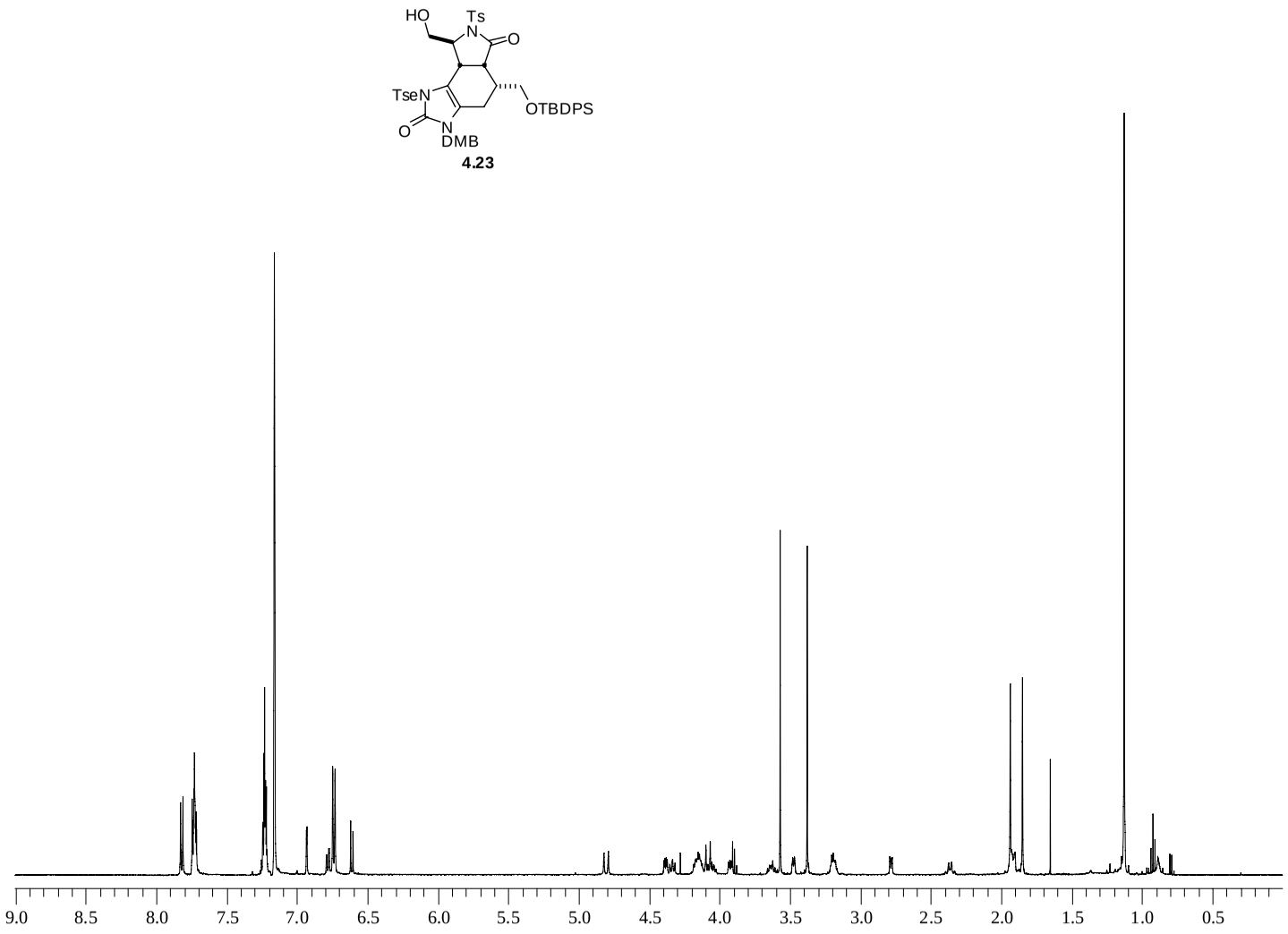
4.19



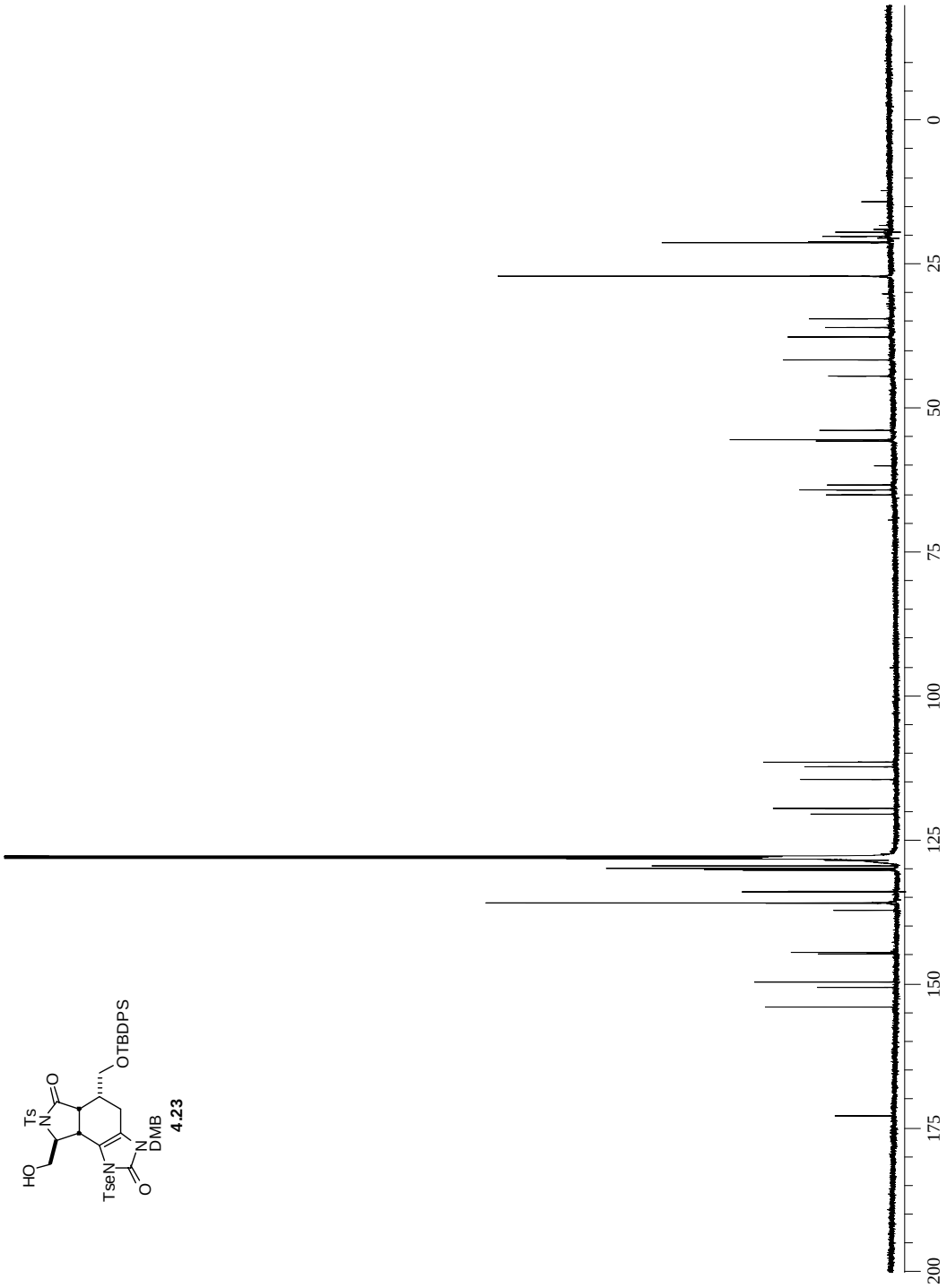
^{13}C-NMR spectrum of pyrrolidine **4.19** (in $CDCl_3$)



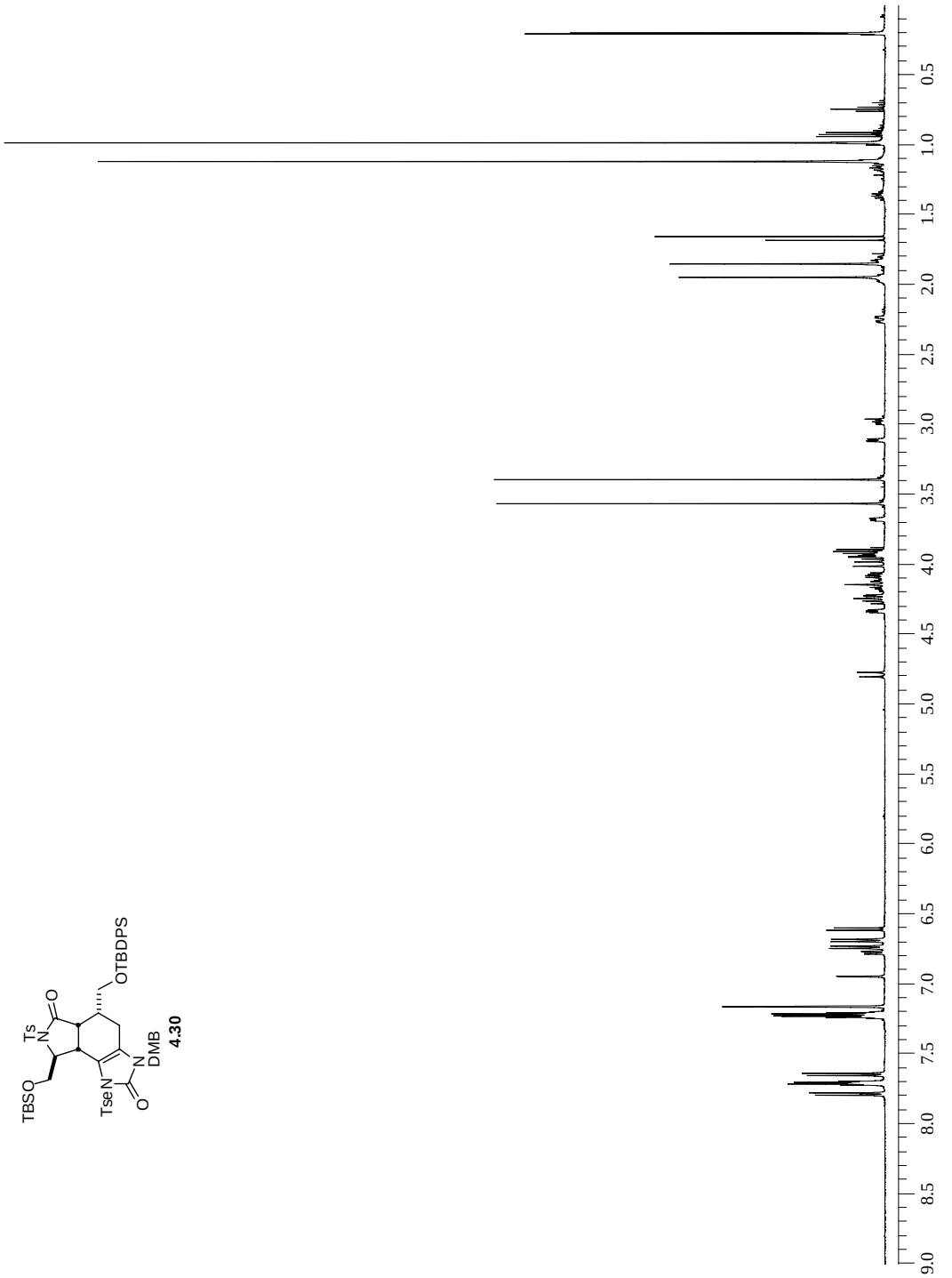
COSY spectrum of pyrrolidine **4.19** (in $CDCl_3$)



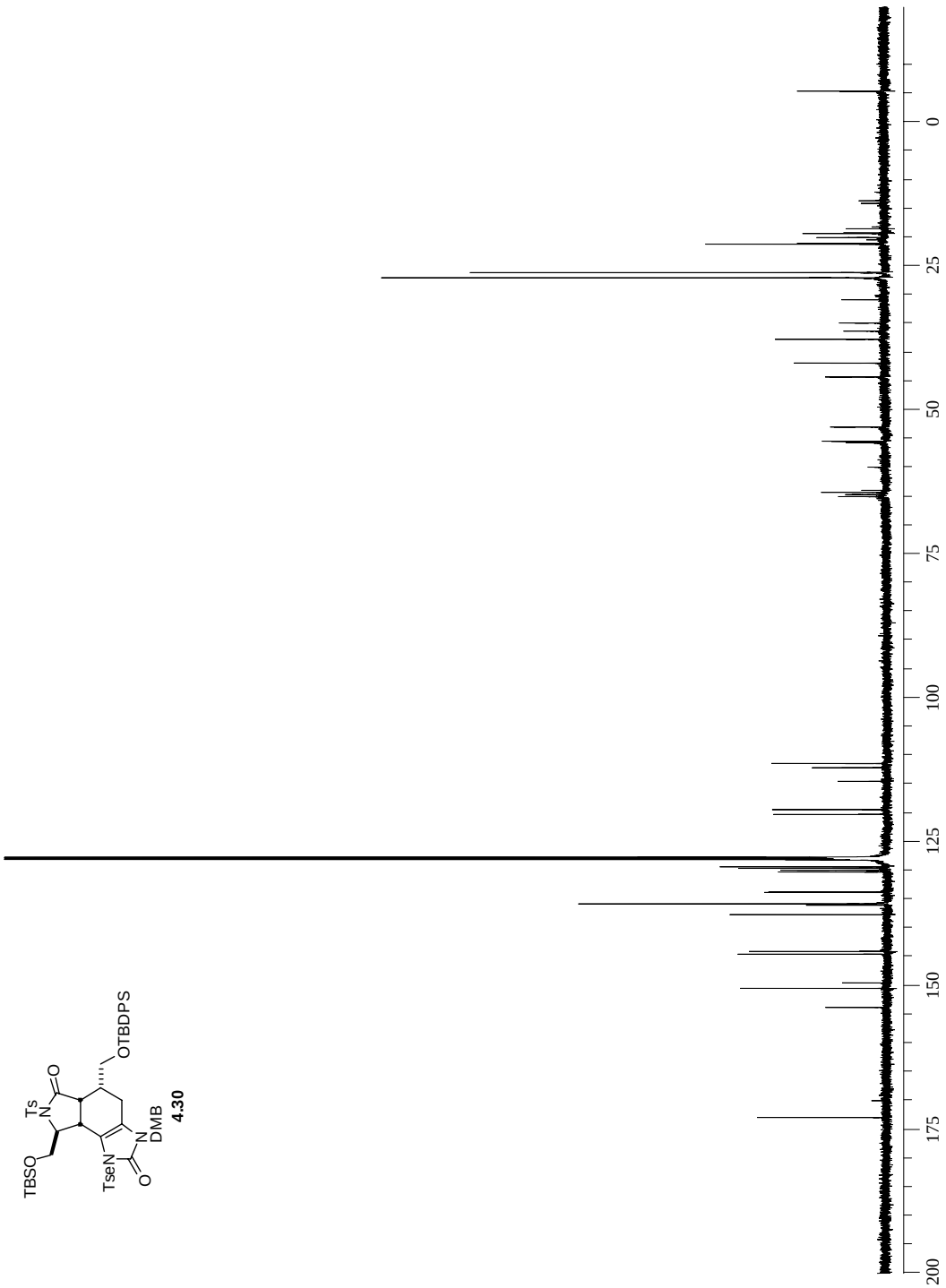
^{1}H-NMR spectrum of alcohol **4.23** (in benzene-d_6)



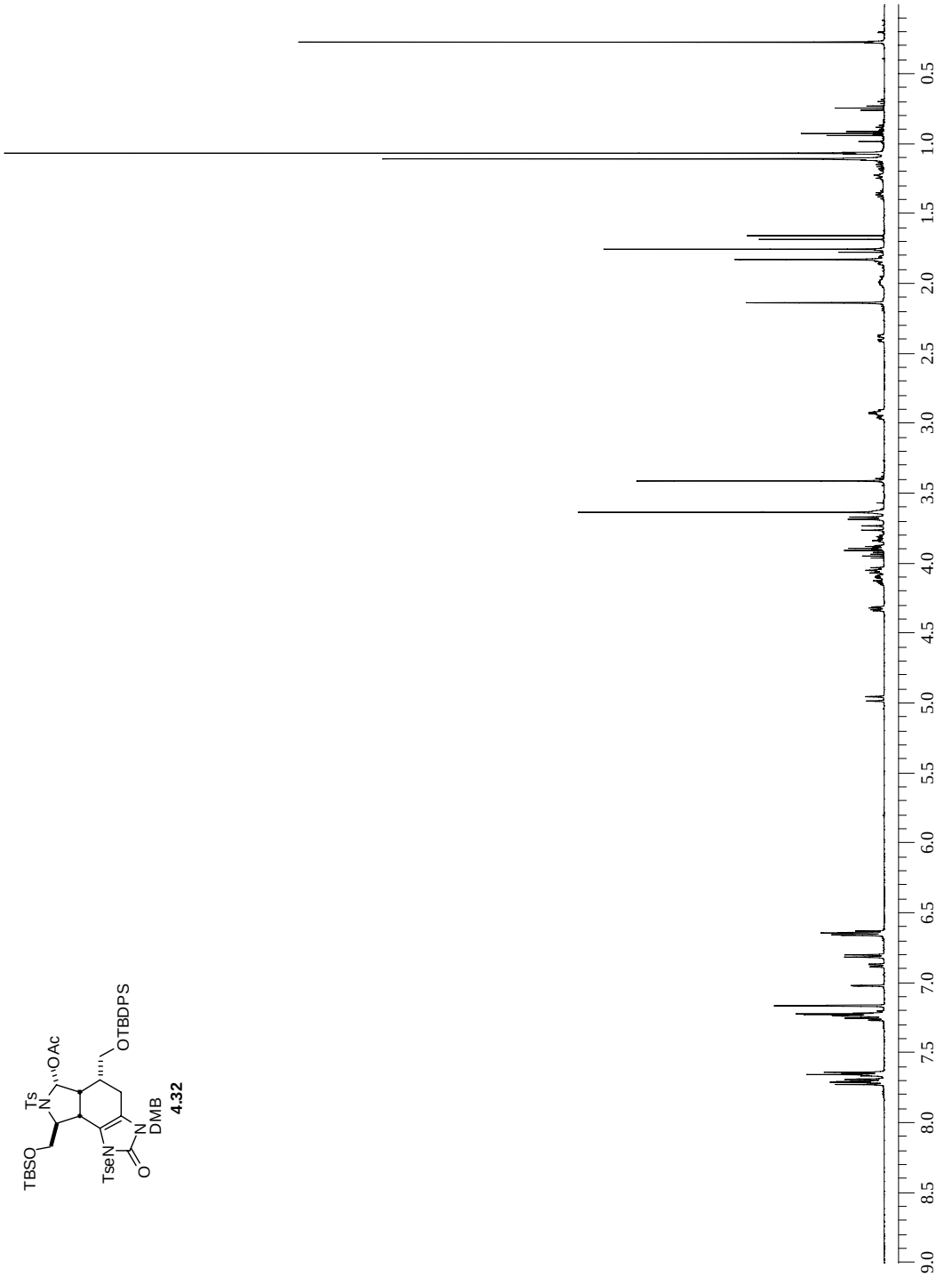
^{13}C-NMR spectrum of alcohol **4.23** (in benzene-d_6)



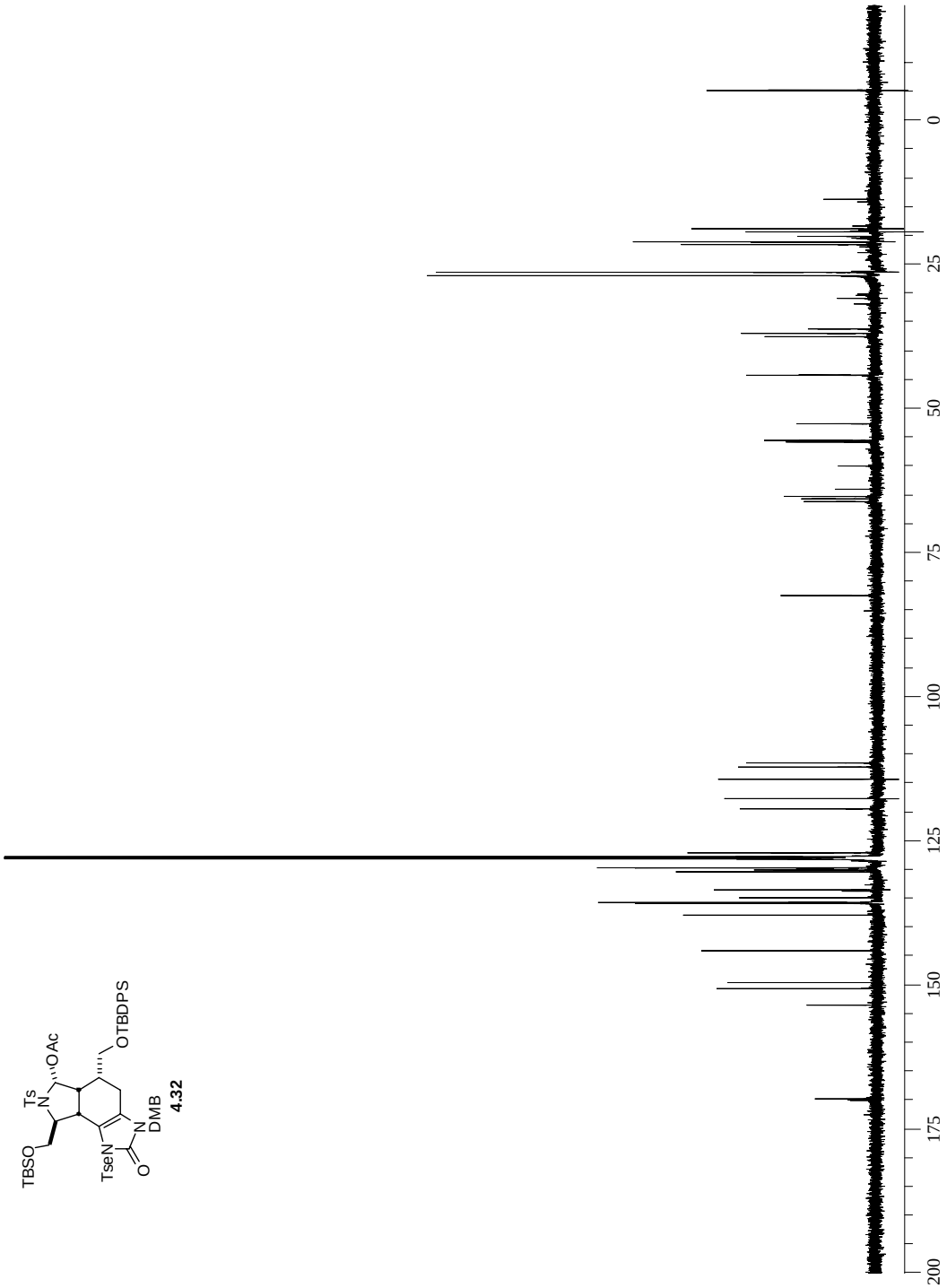
^{1}H-NMR spectrum of lactam **4.30** (in benzene-d_6)



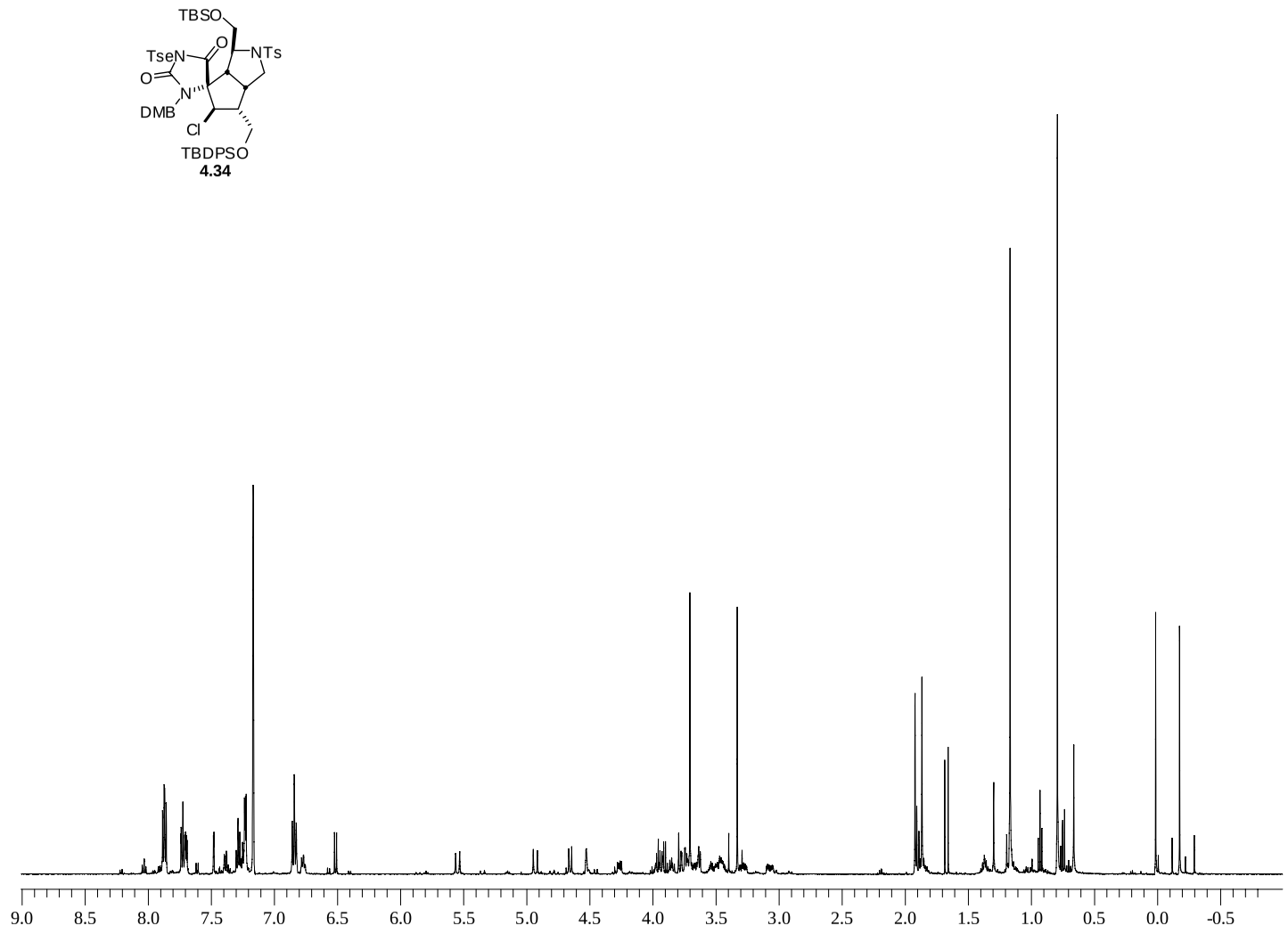
^{13}C-NMR spectrum of lactam **4.30** (in benzene-d_6)



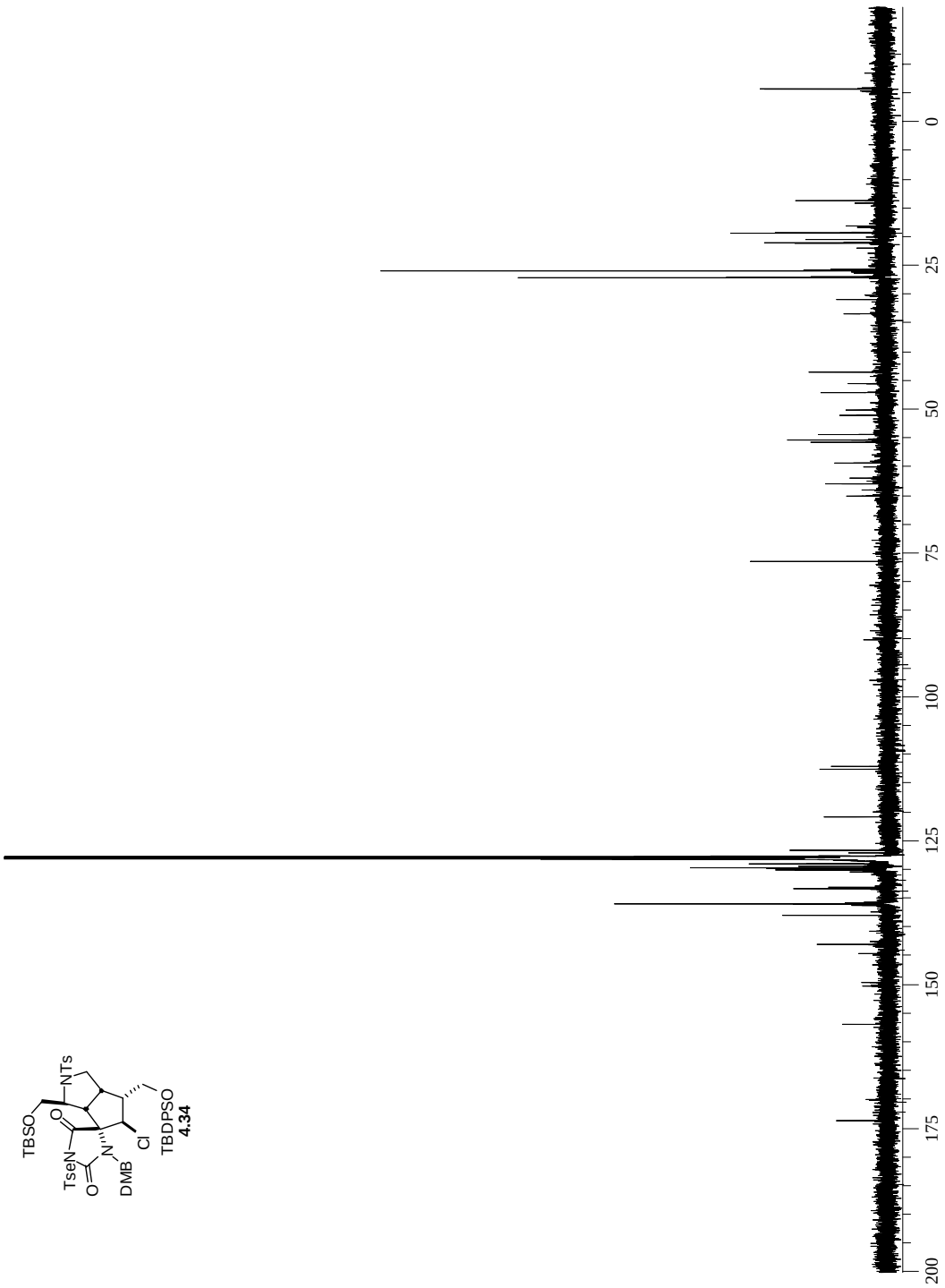
^{1}H-NMR spectrum of acetate **4.32** (in benzene-d_6)



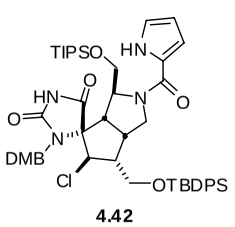
^{13}C-NMR spectrum of acetate **4.32** (in benzene-d_6)



^{1}H-NMR spectrum of chlorocyclopentane **4.34** (in benzene-d_6)

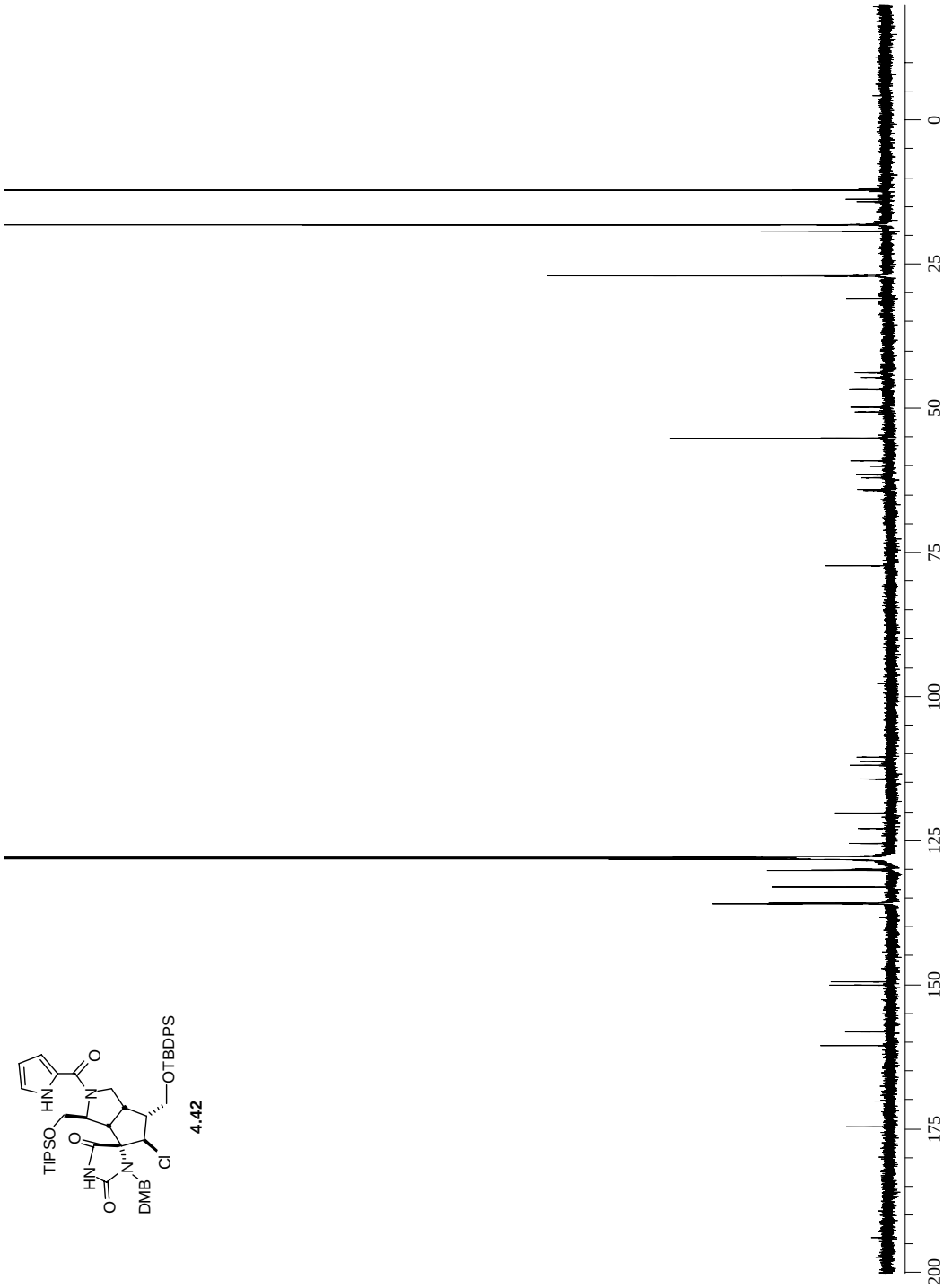


^{13}C-NMR spectrum of chlorocyclopentane **4.34** (in benzene-d_6)

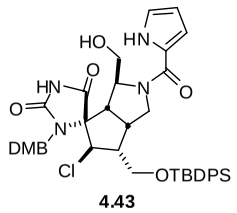


4.42

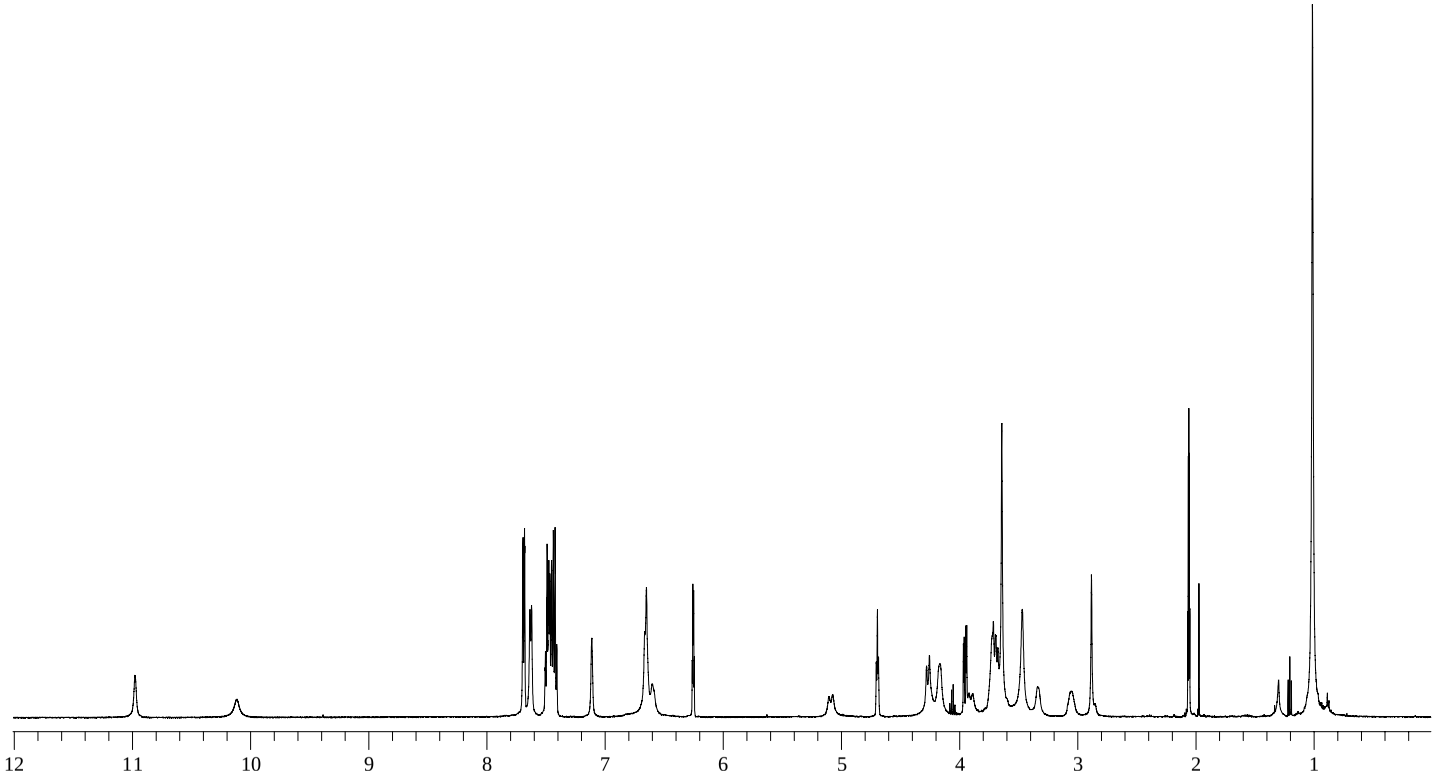
^{1}H-NMR spectrum of pyrrole **4.42** (in benzene-d_6)



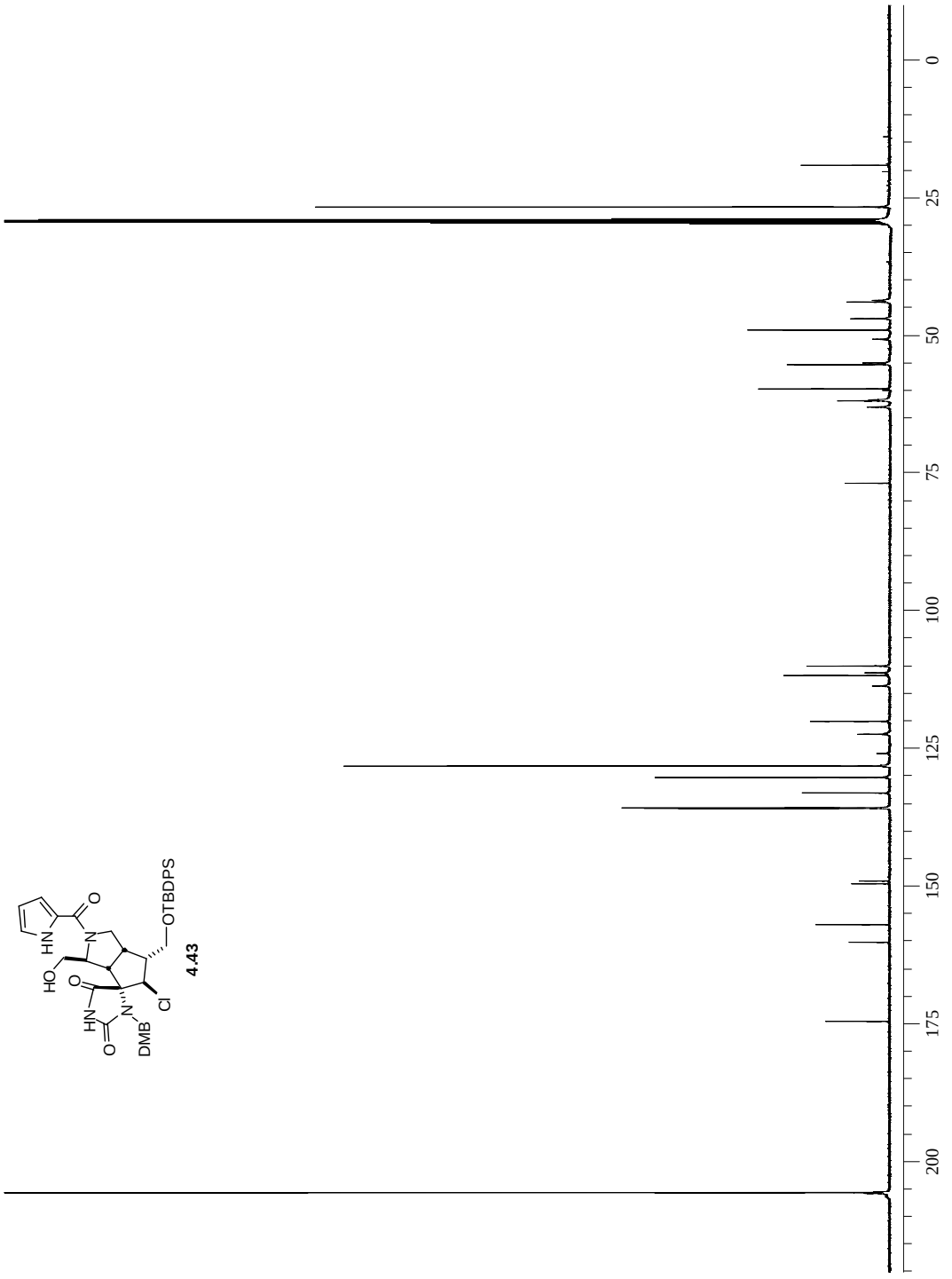
^{13}C-NMR spectrum of pyrrole **4.42** (in benzene-d_6)



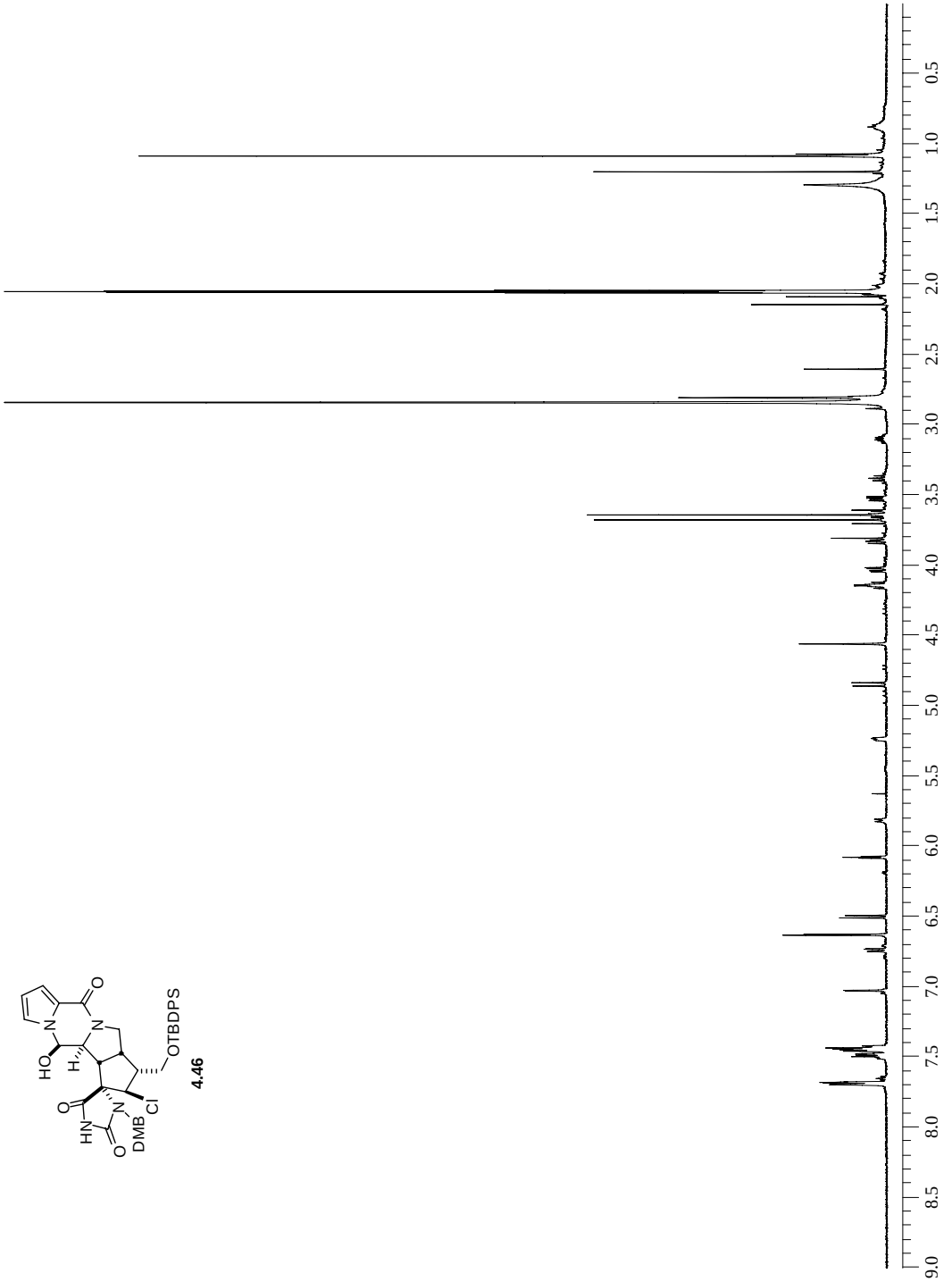
4.43



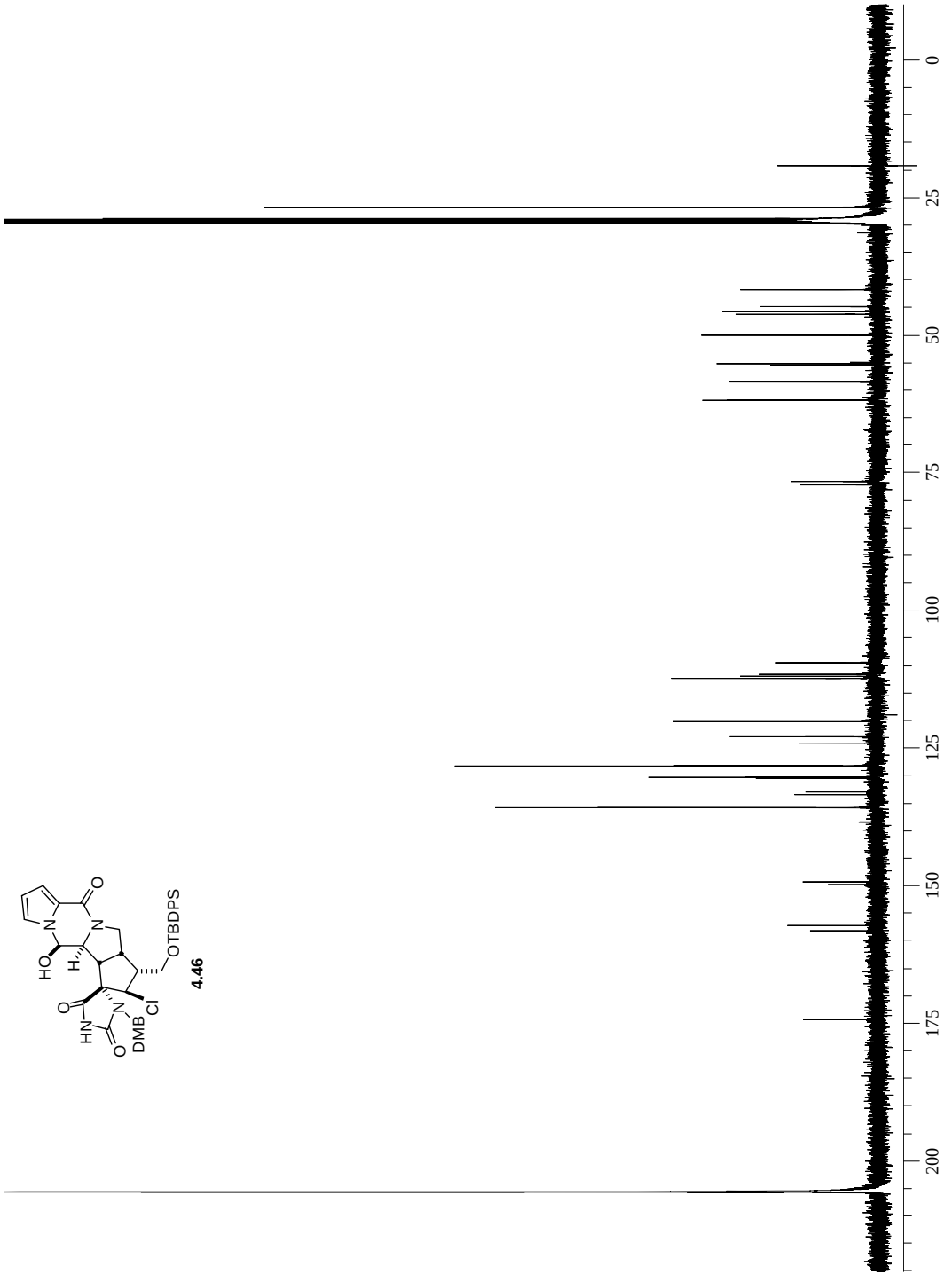
^{1}H-NMR spectrum of alcohol **4.43** (in acetone-d_6)



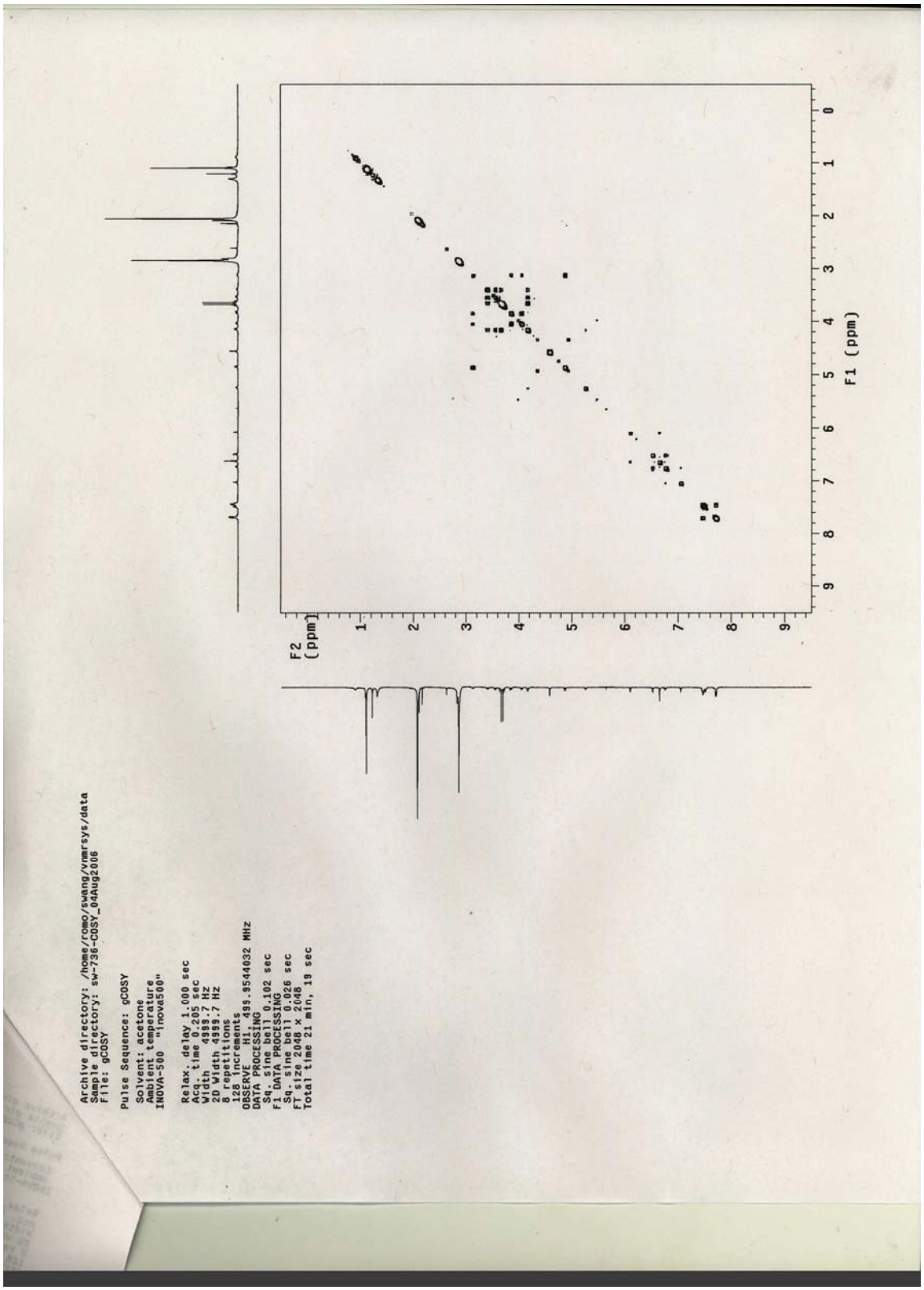
^{13}C-NMR spectrum of alcohol **4.43** (in acetone-d_6)



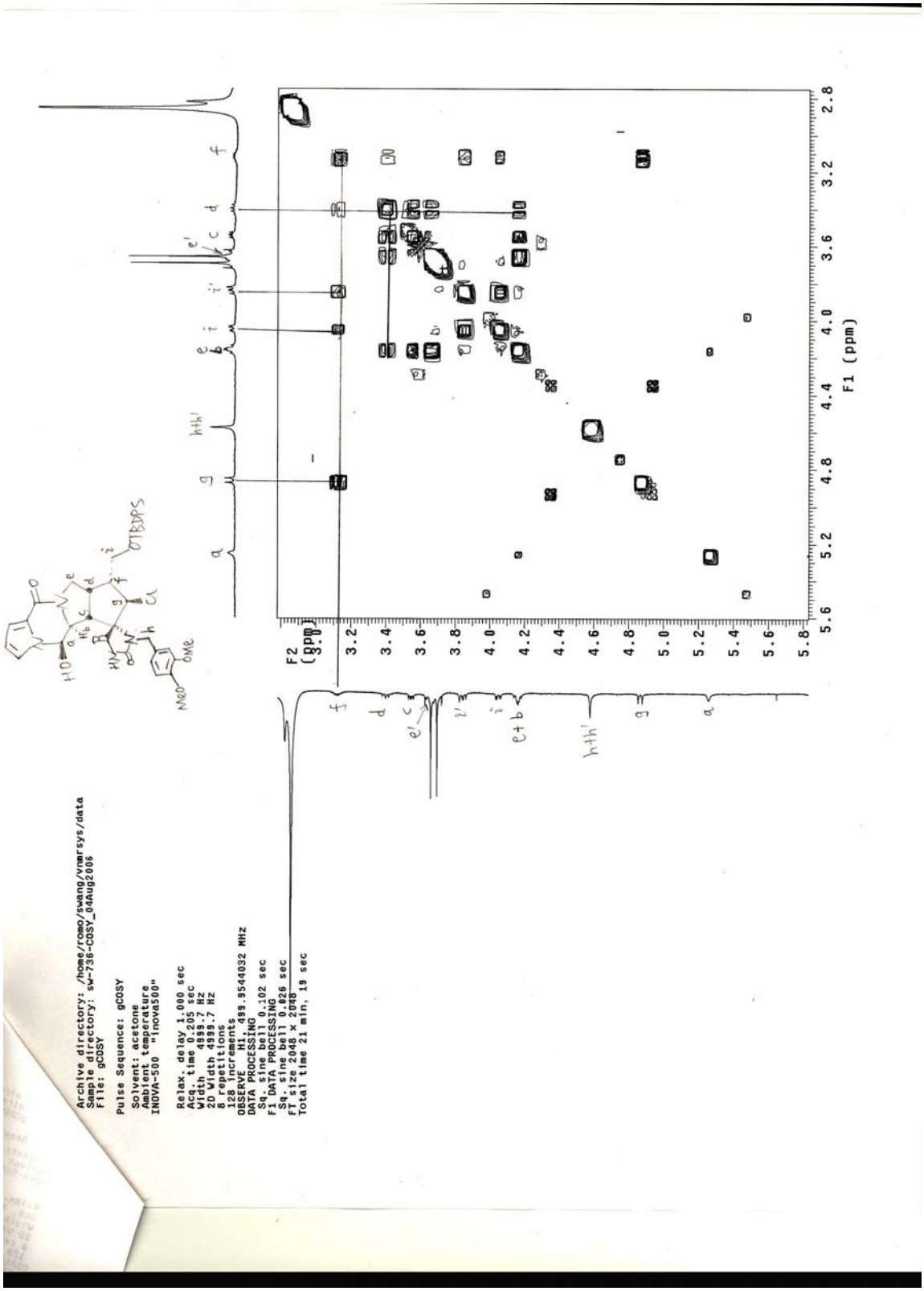
^{1}H-NMR spectrum of *N*,*O*-acetal **4.46** (in acetone-d_6)



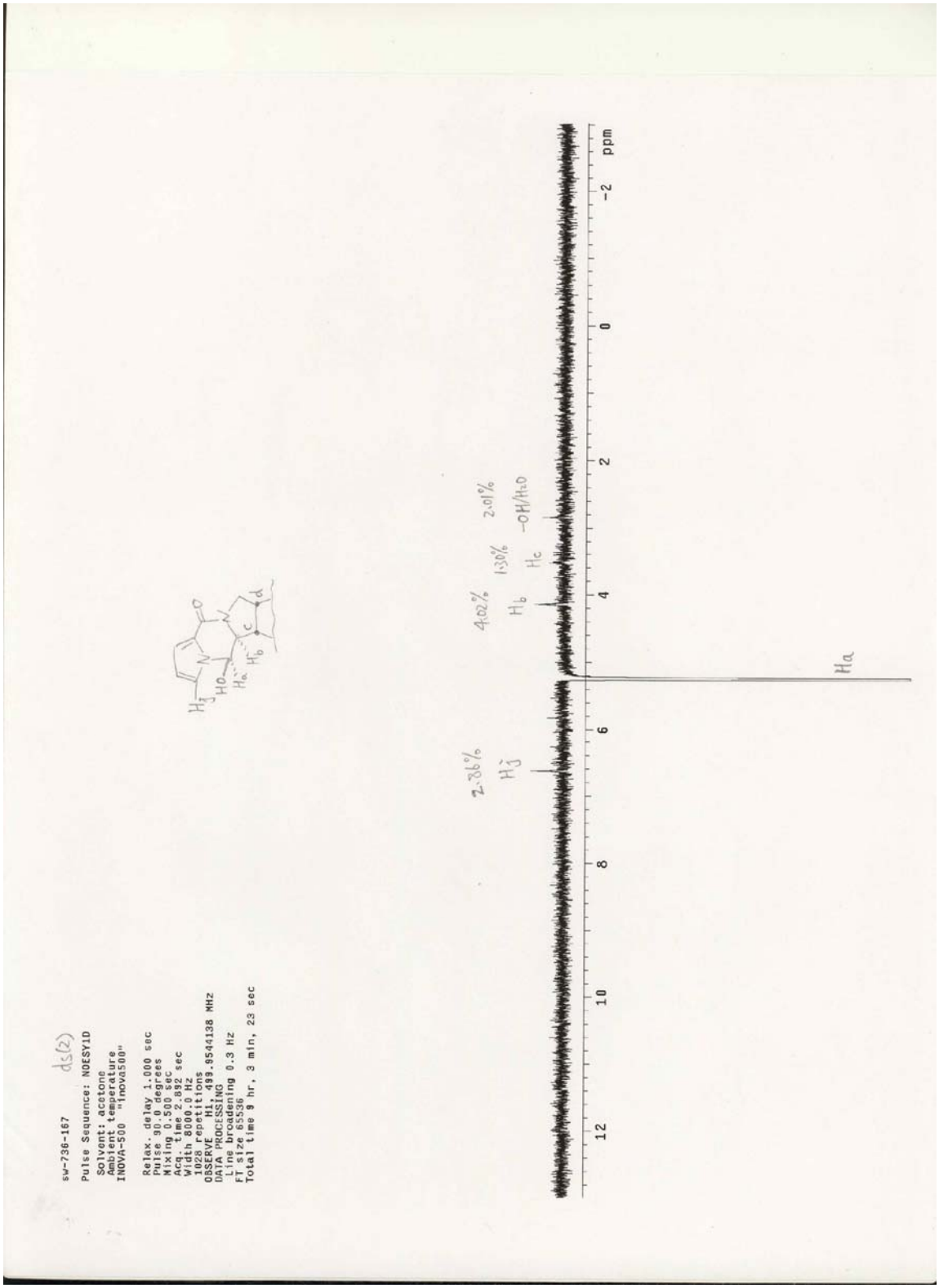
^{13}C-NMR spectrum of *N,O*-acetal **4.46** (in acetone-d_6)



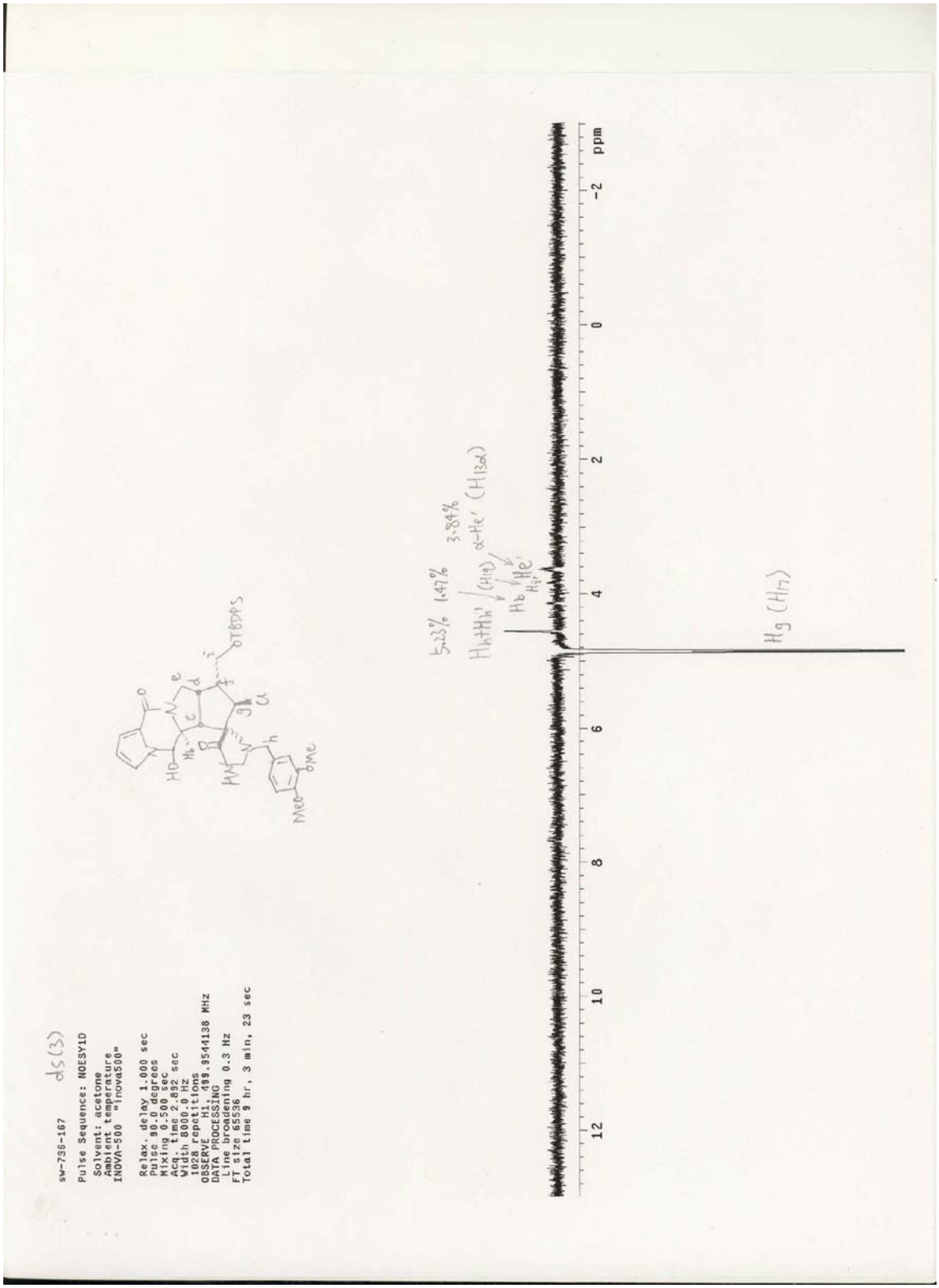
COSY spectrum of *N,O*-acetal **4.46** (in acetone-d_6)



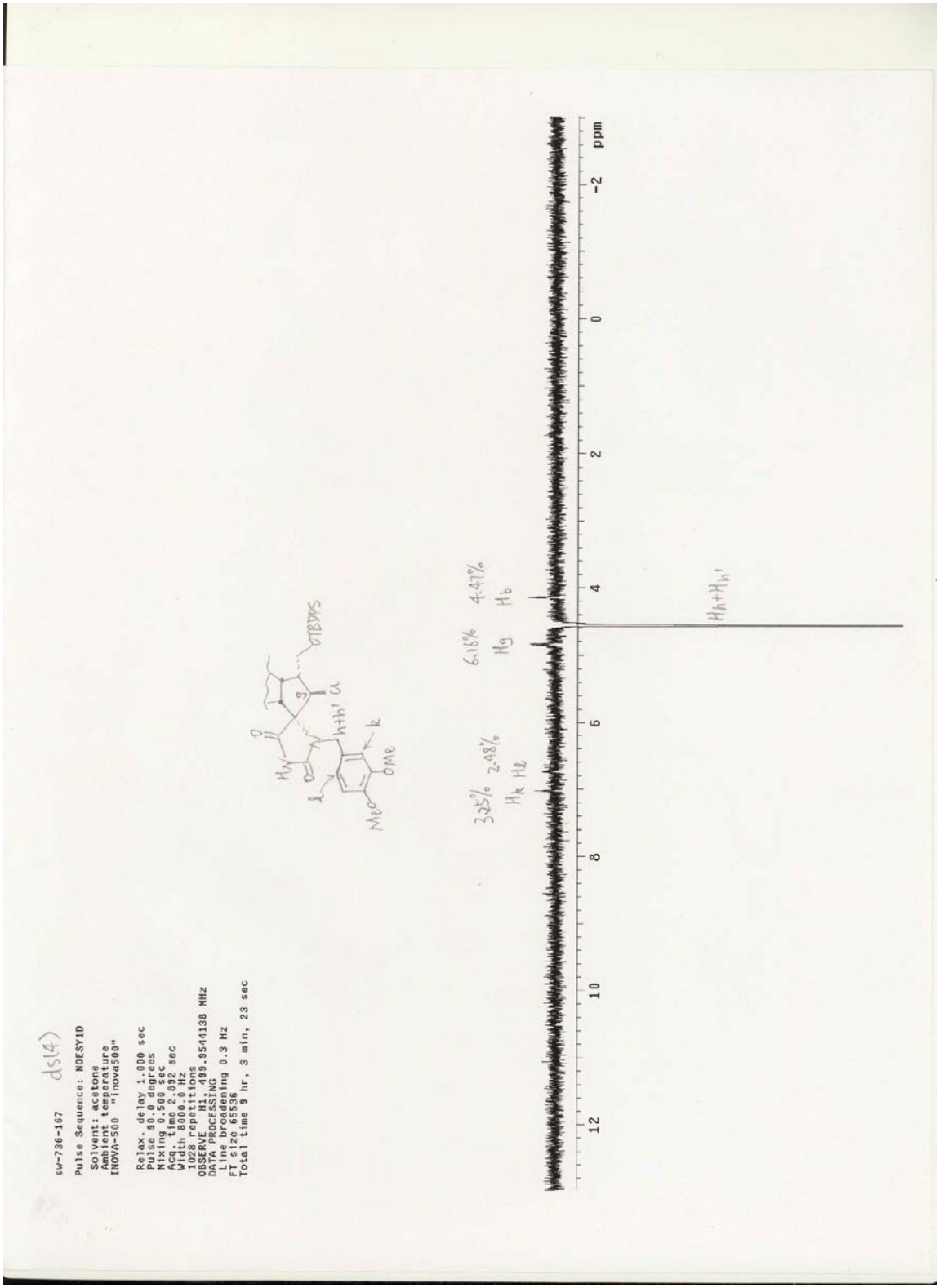
COSY spectrum of *N,O*-acetal **4.46** (in acetone-d_6)



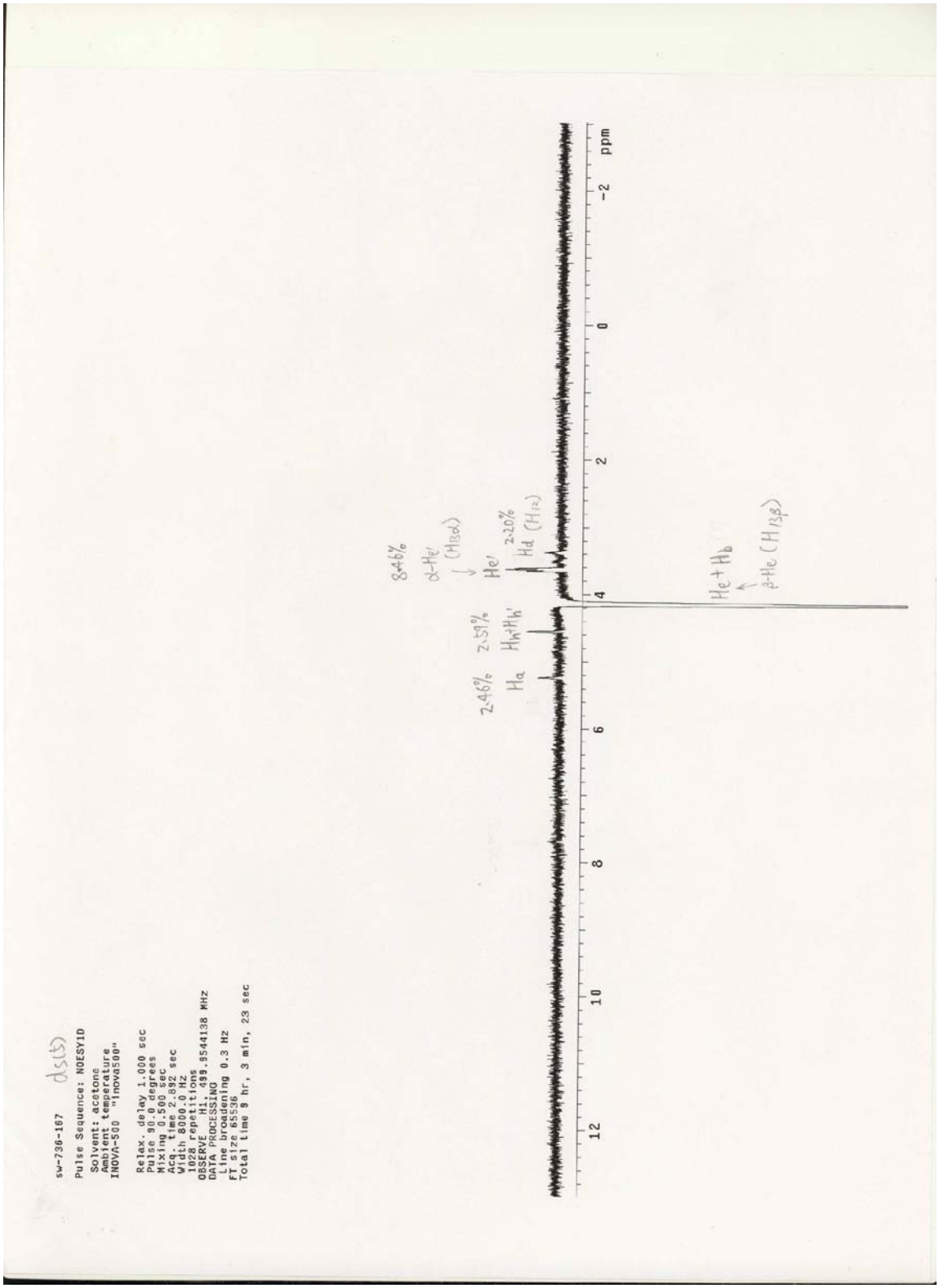
NOESY spectrum of *N,O*-acetal **4.46** (in acetone-d_6)



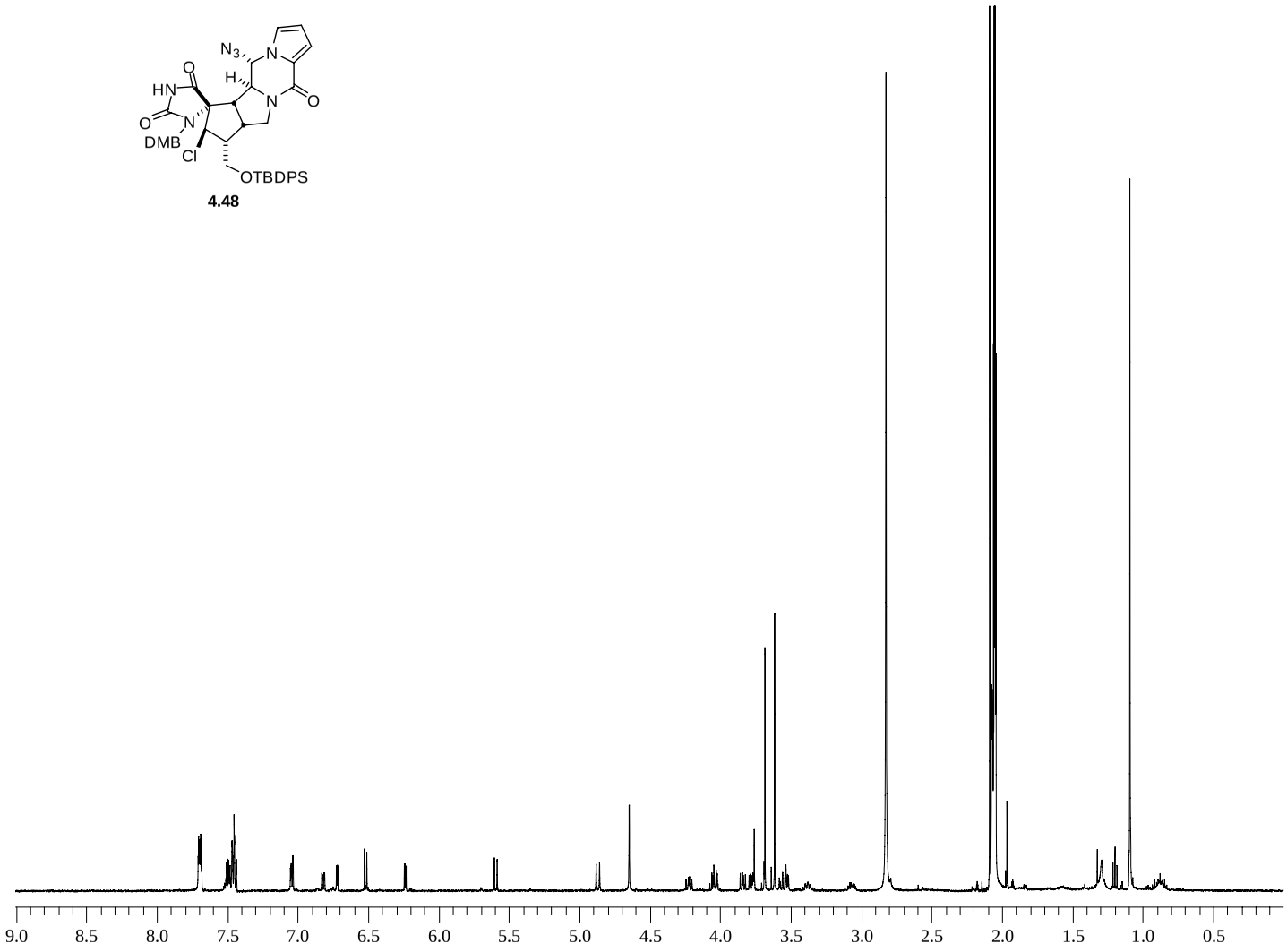
NOESY spectrum of *N,O*-acetal **4.46** (in acetone-d_6)



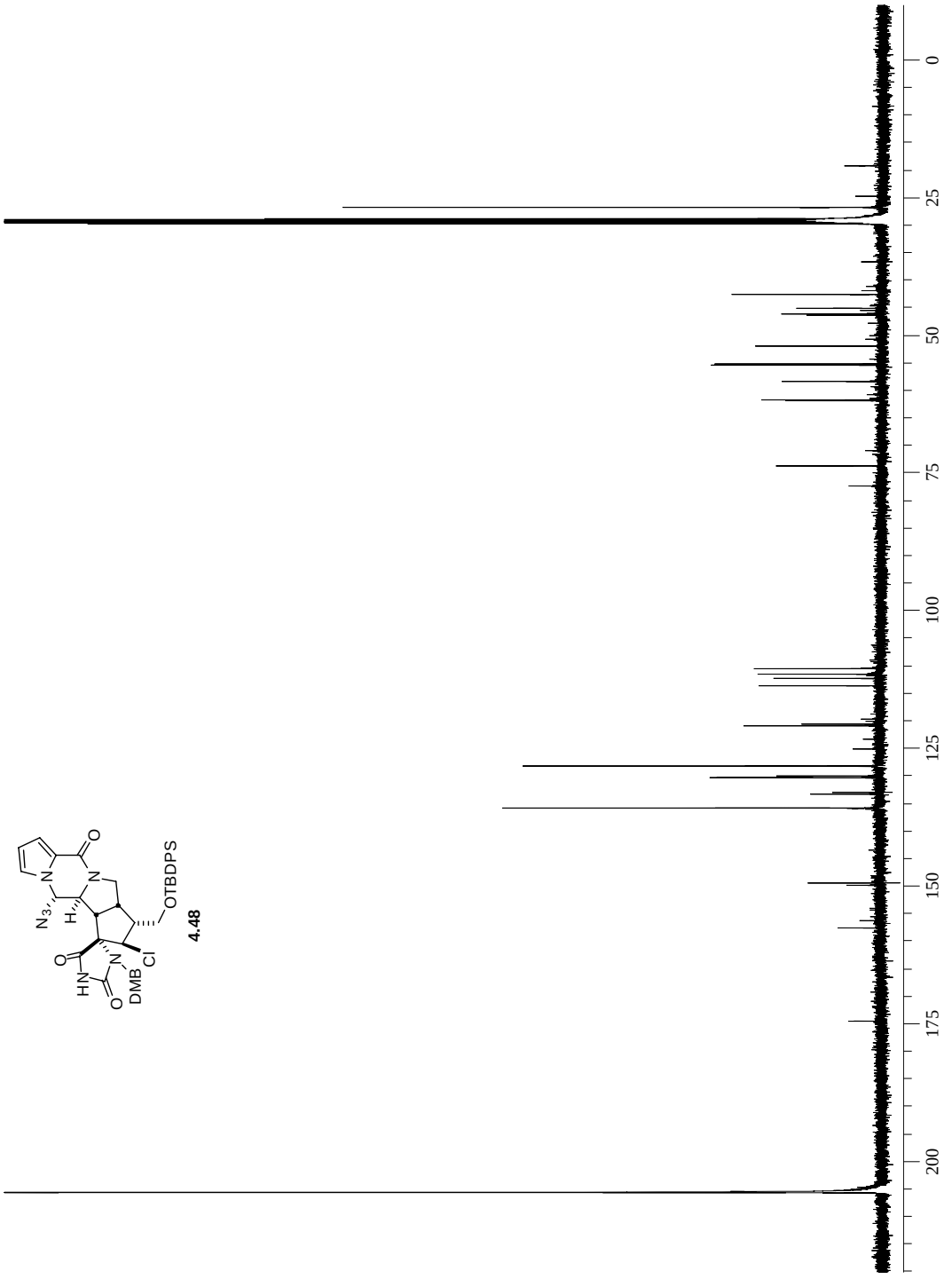
NOESY spectrum of *N,O*-acetal **4.46** (in acetone-d_6)



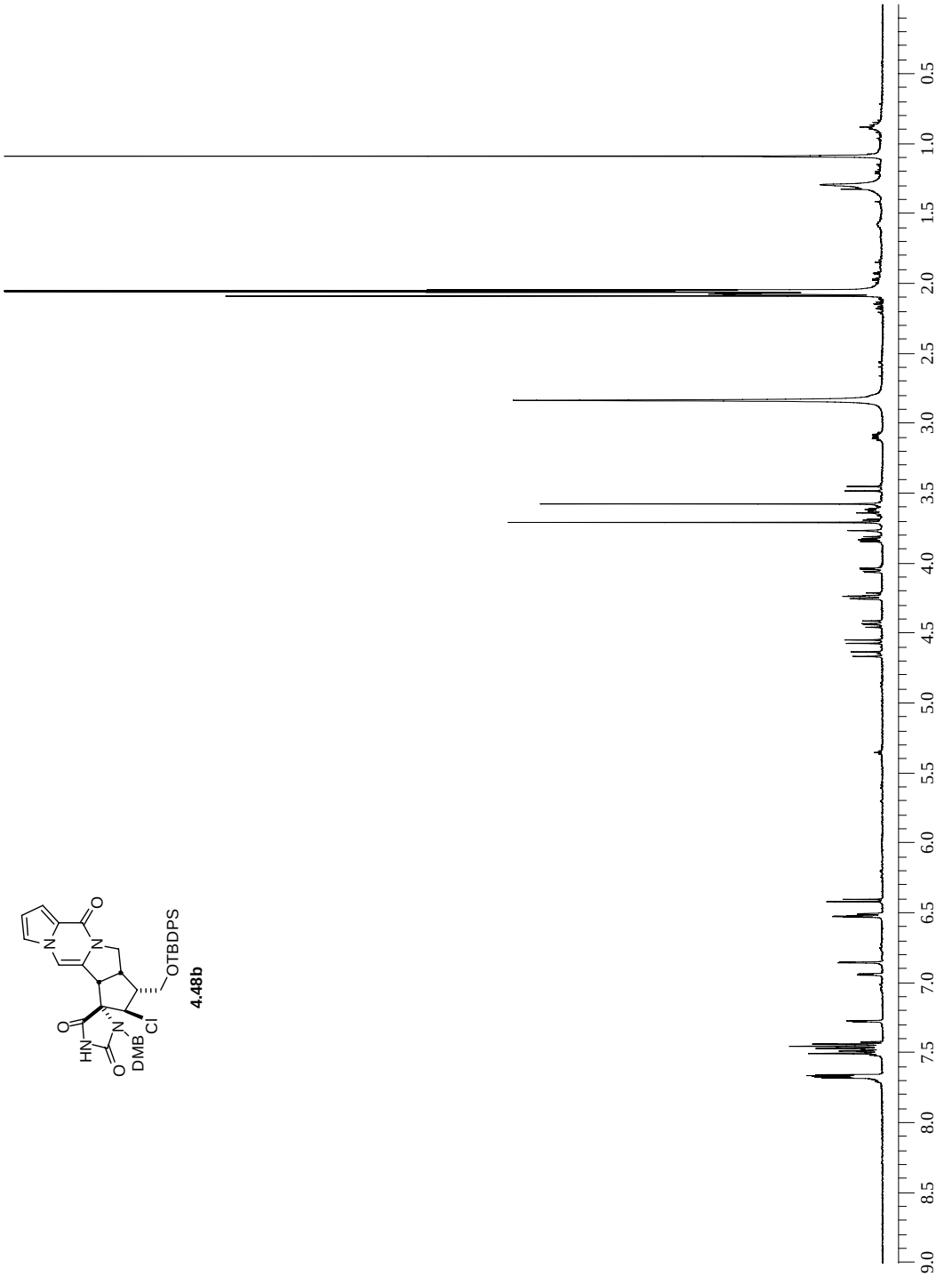
NOESY spectrum of *N,O*-acetal **4.46** (in acetone-d_6)



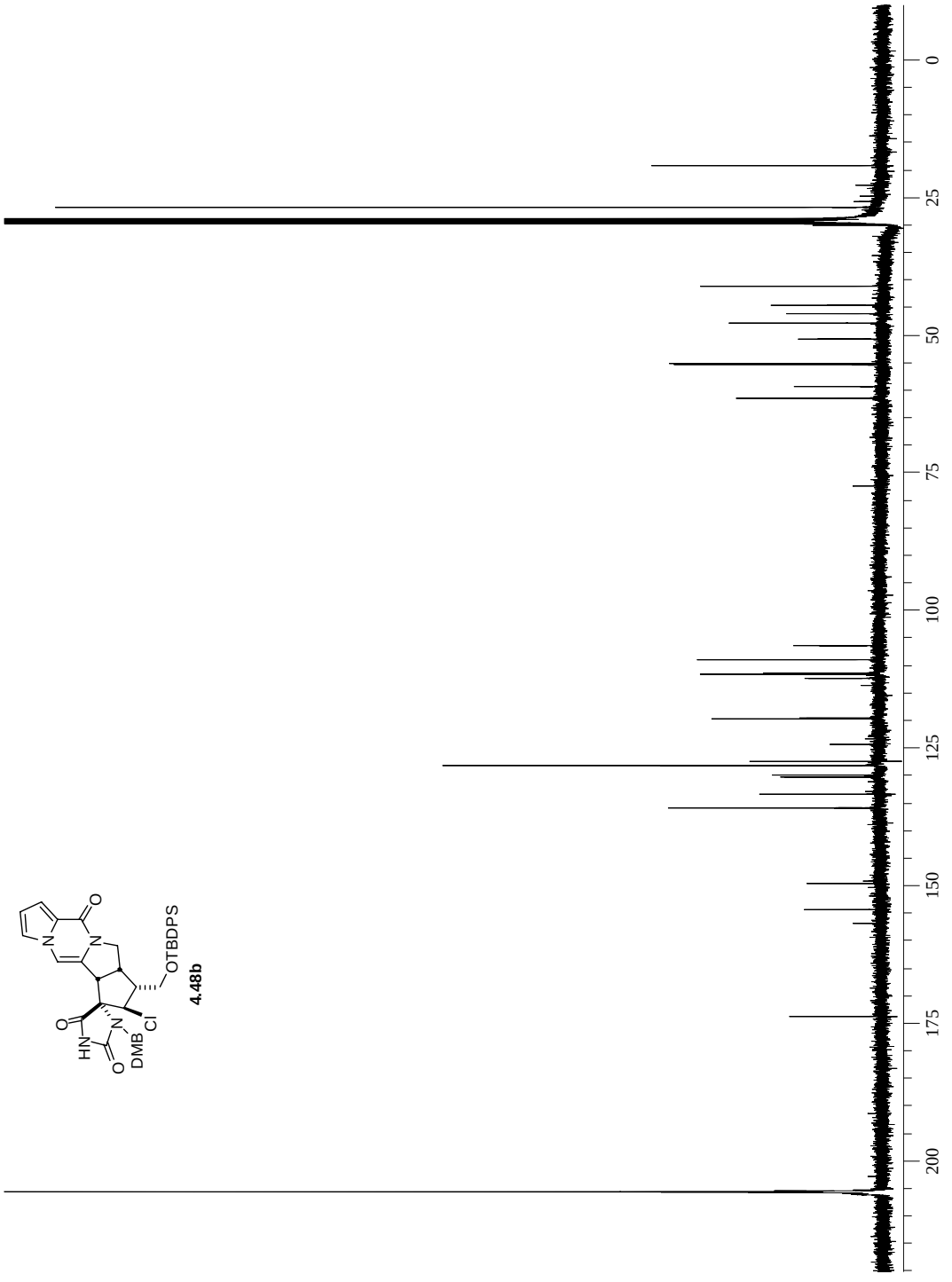
^{1}H-NMR spectrum of azide **4.48** (in acetone-d_6)



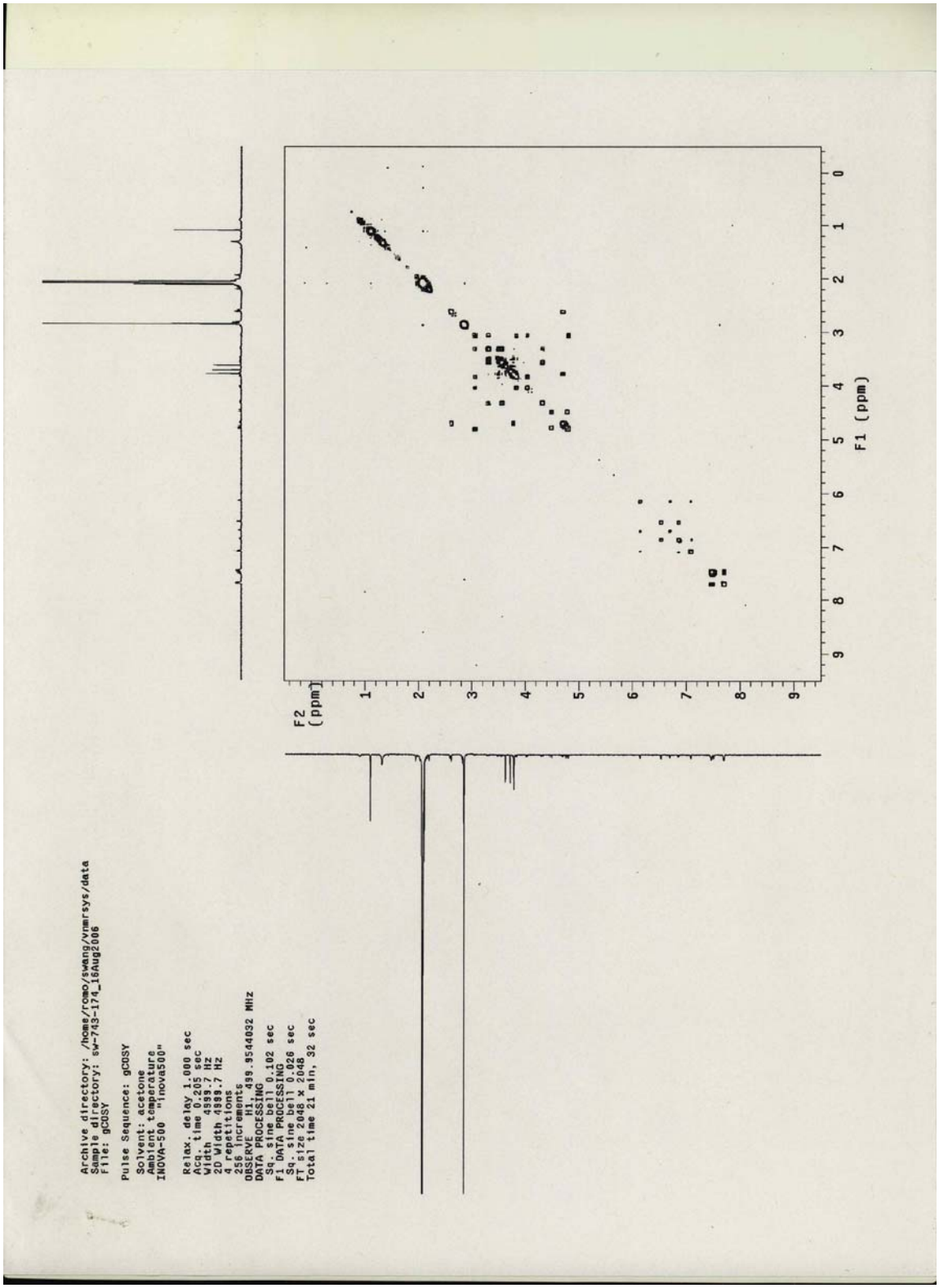
^{13}C-NMR spectrum of azide **4.48** (in acetone-d_6)



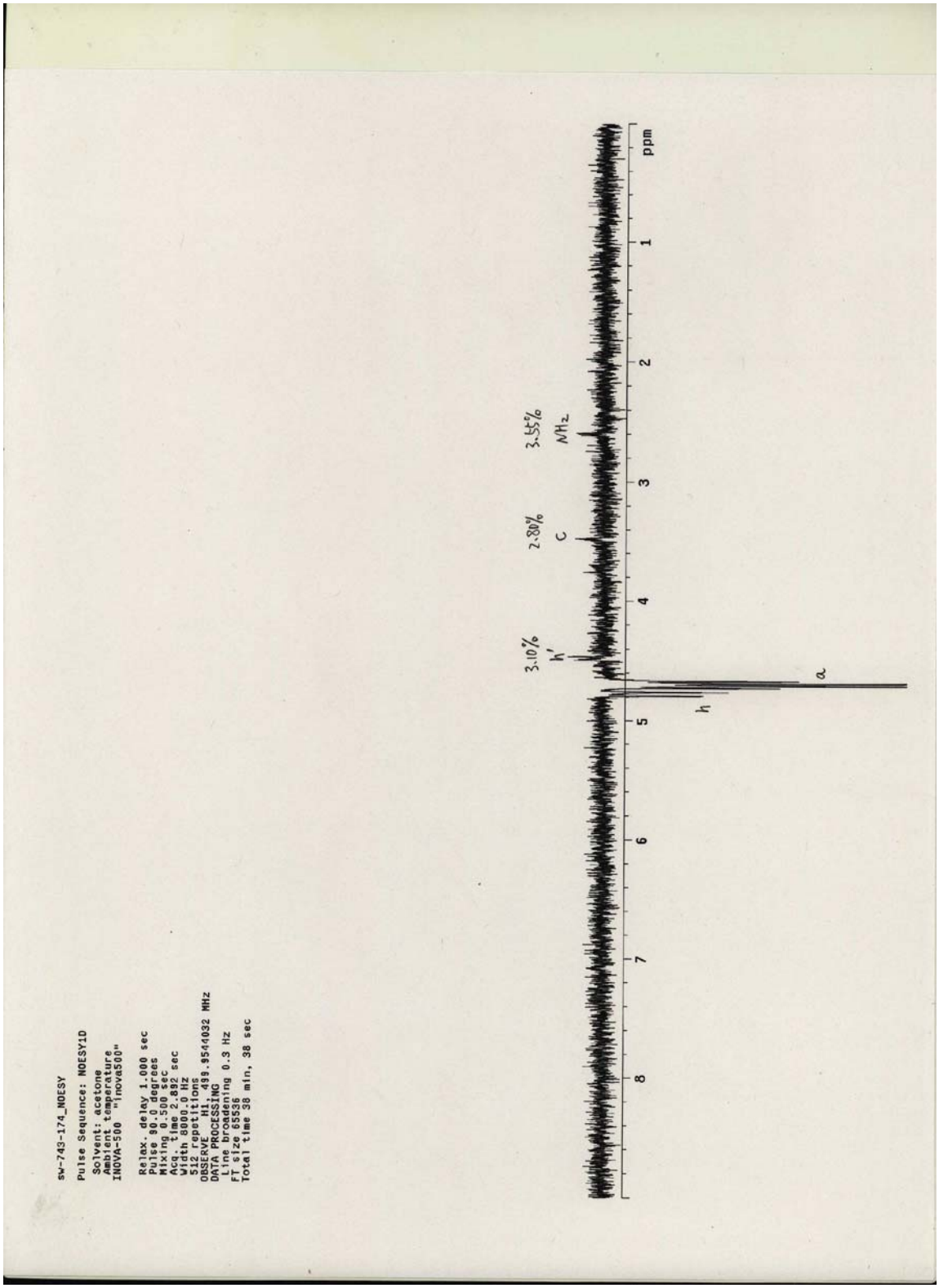
^{1}H-NMR spectrum of pyrrolo-pyrazinone **4.48b** (in acetone-d_6)



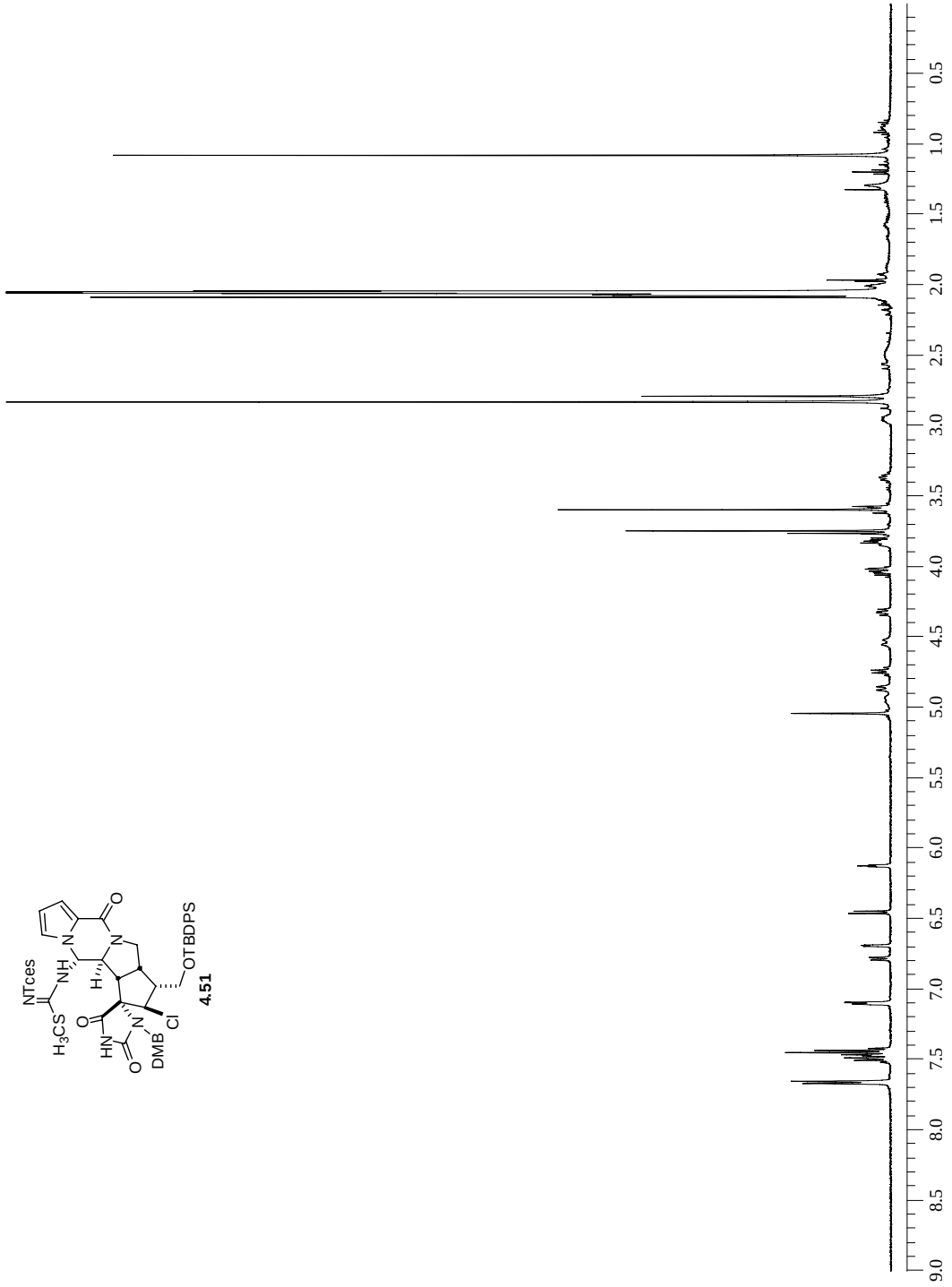
^{13}C-NMR spectrum of pyrrolo-pyrazinone **4.48b** (in acetone-d_6)



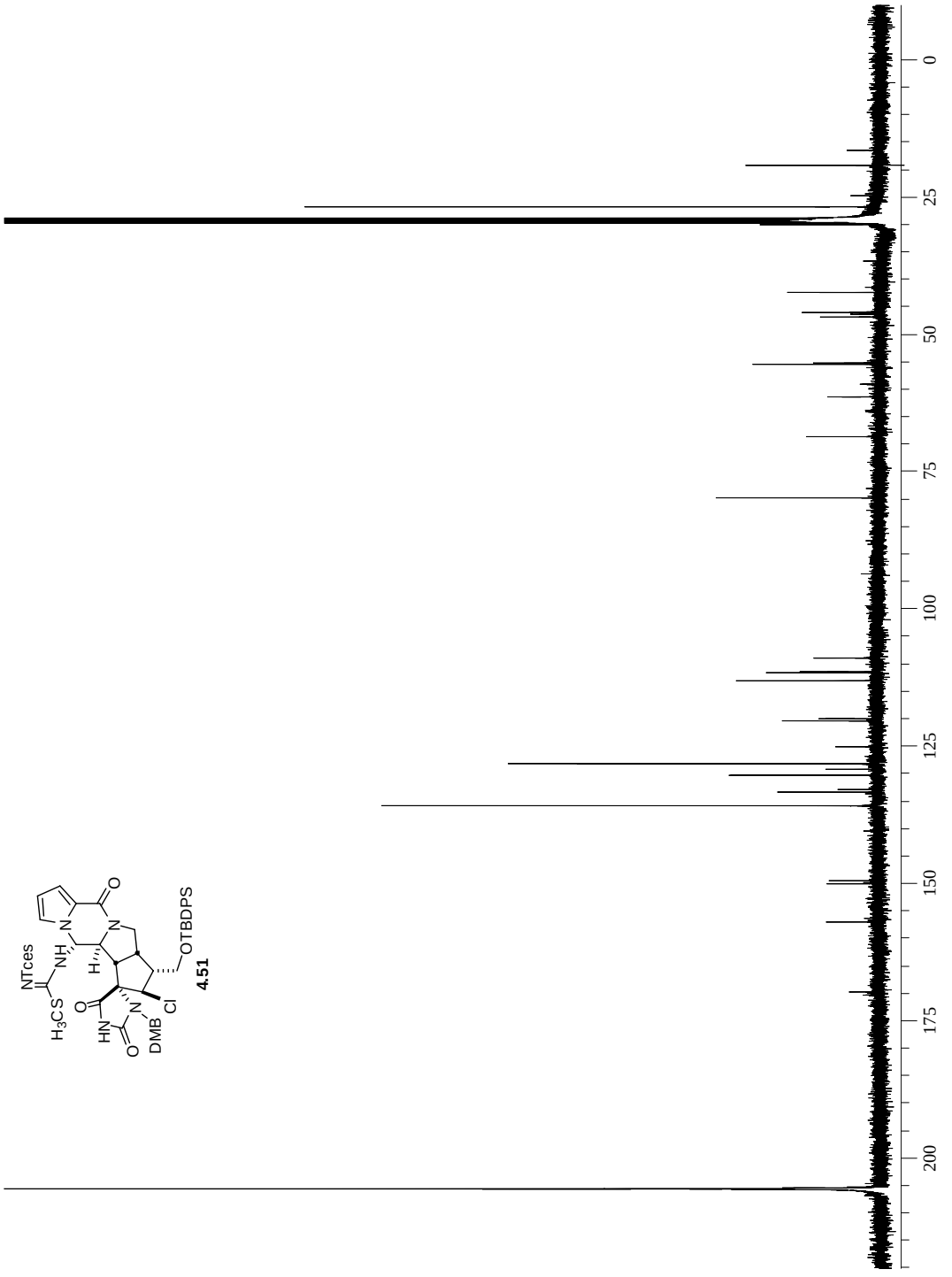
COSY spectrum of aminal **4.49** (in acetone-d_6)



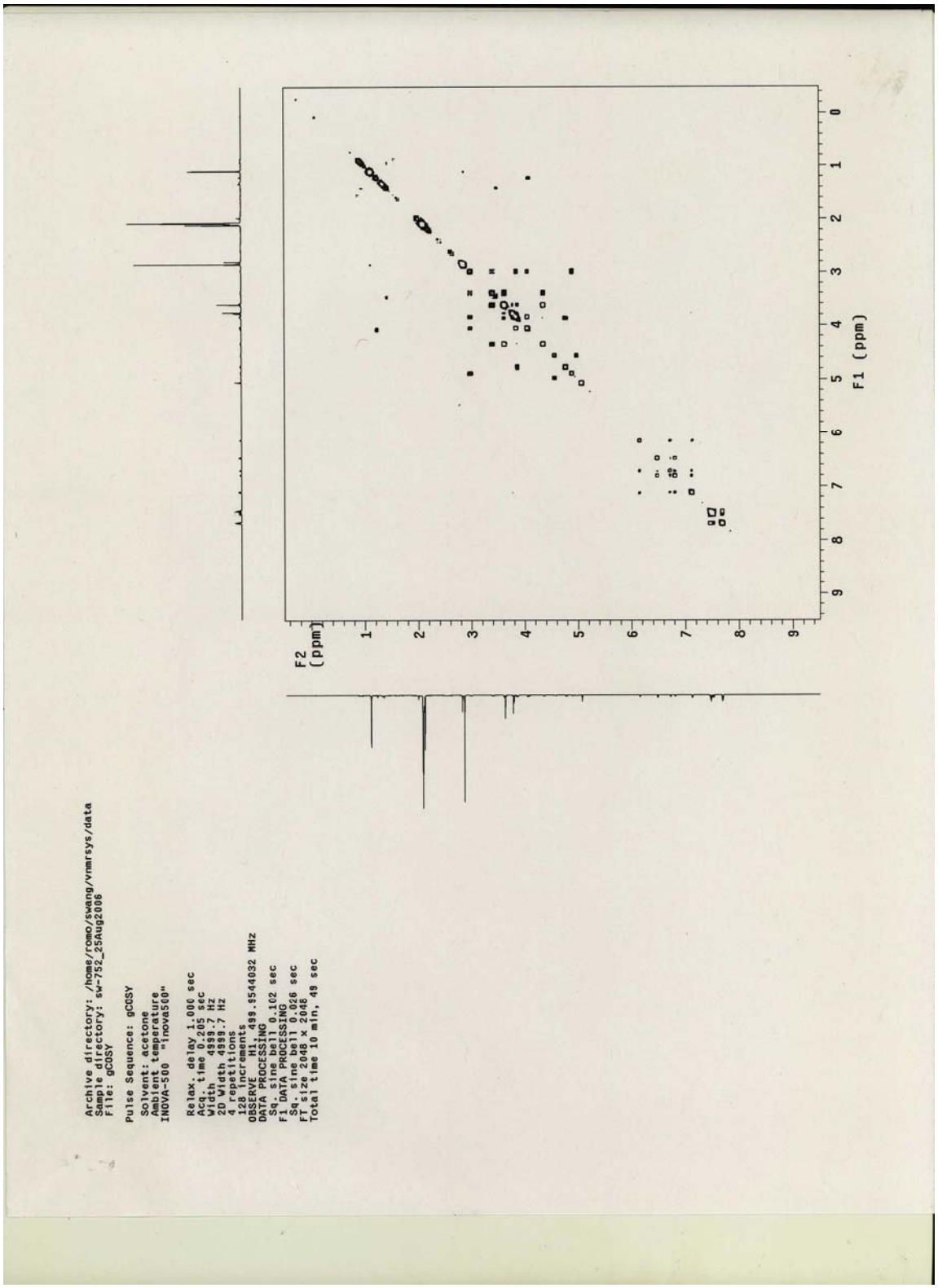
NOESY spectrum of aminal **4.49** (in acetone-d_6)



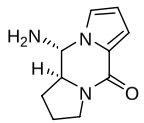
^{1}H-NMR spectrum of isothiourea **4.51** (in acetone-d_6)



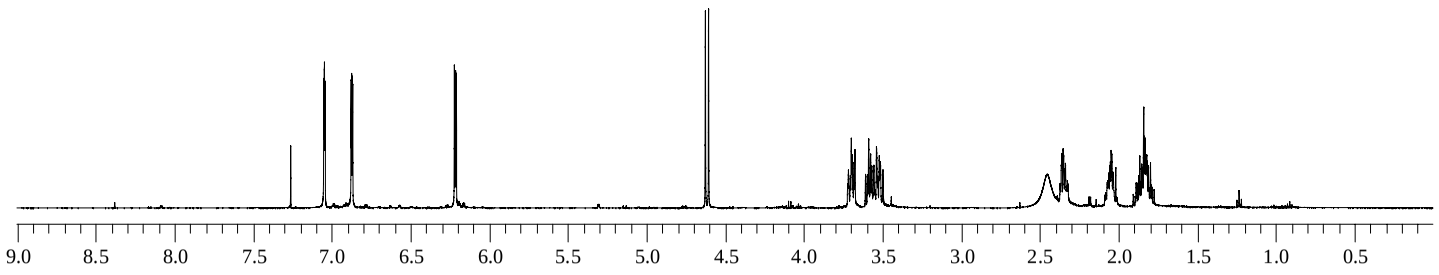
^{13}C-NMR spectrum of isothiourea **4.51** (in acetone-d_6)



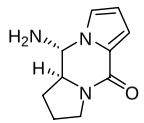
COSY spectrum of isothiourea **4.51** (in acetone-d_6)



5.14



^{1}H-NMR spectrum of aminal **5.14** (in $CDCl_3$)



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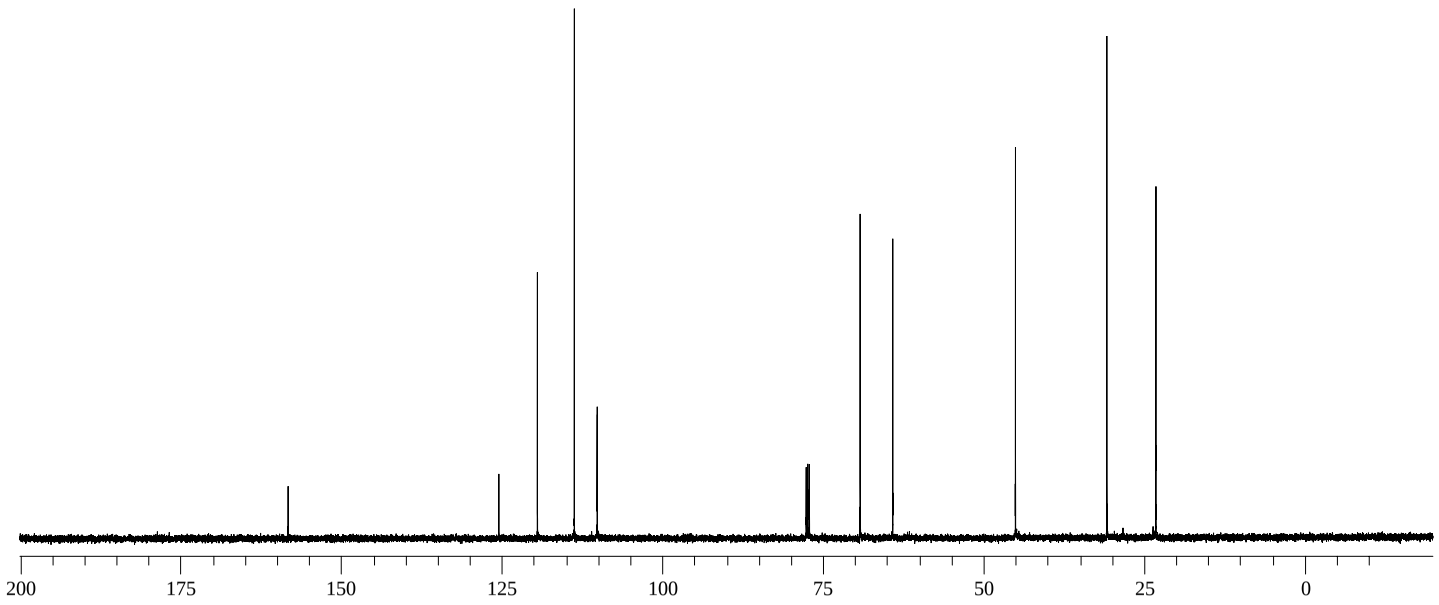
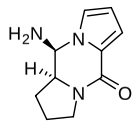
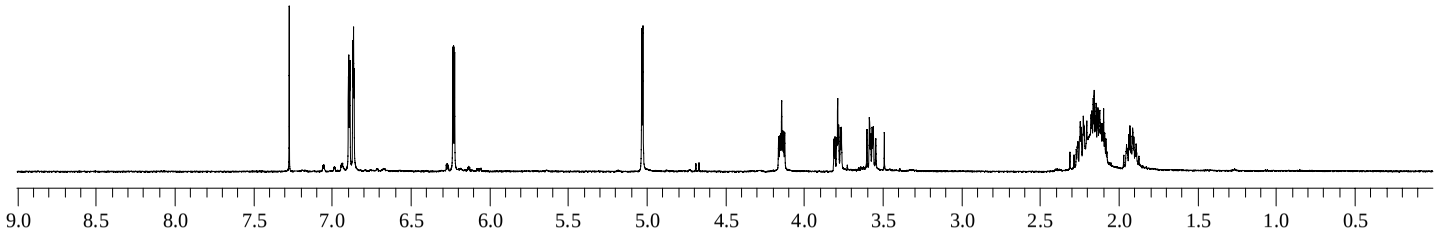


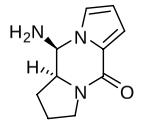
^{13}C-NMR spectrum of aminal **5.14** (in $CDCl_3$)



5.15



^{1}H-NMR spectrum of aminal **5.15** (in $CDCl_3$)



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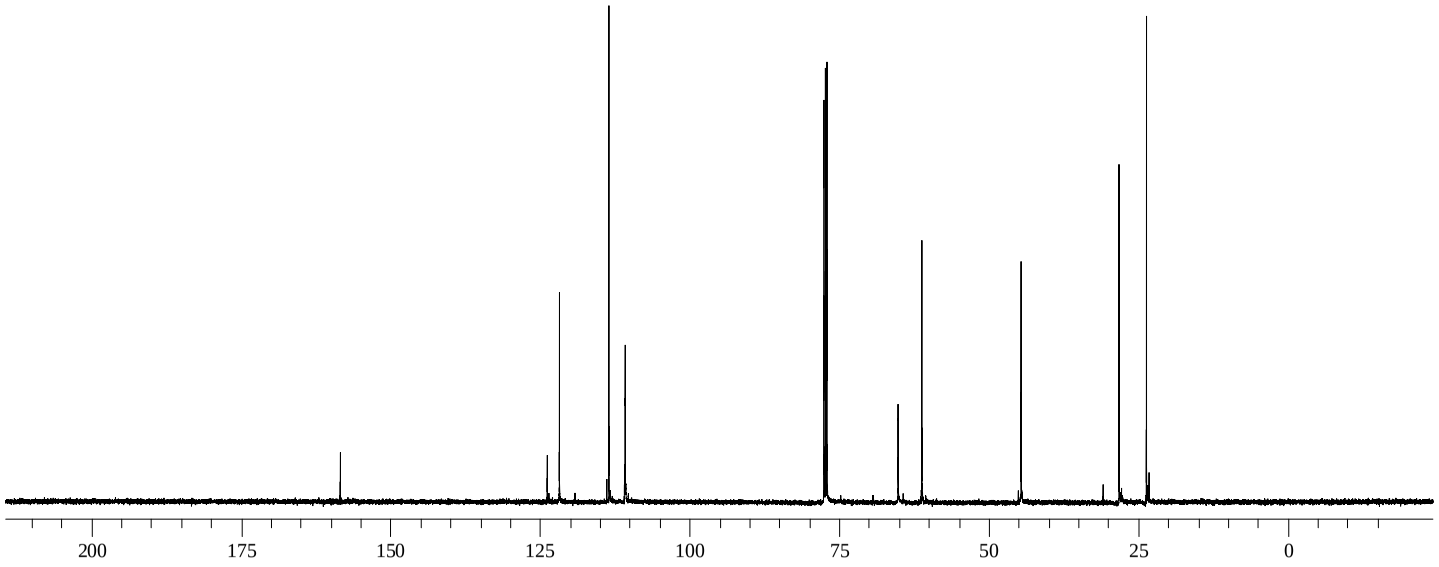
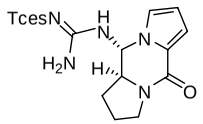
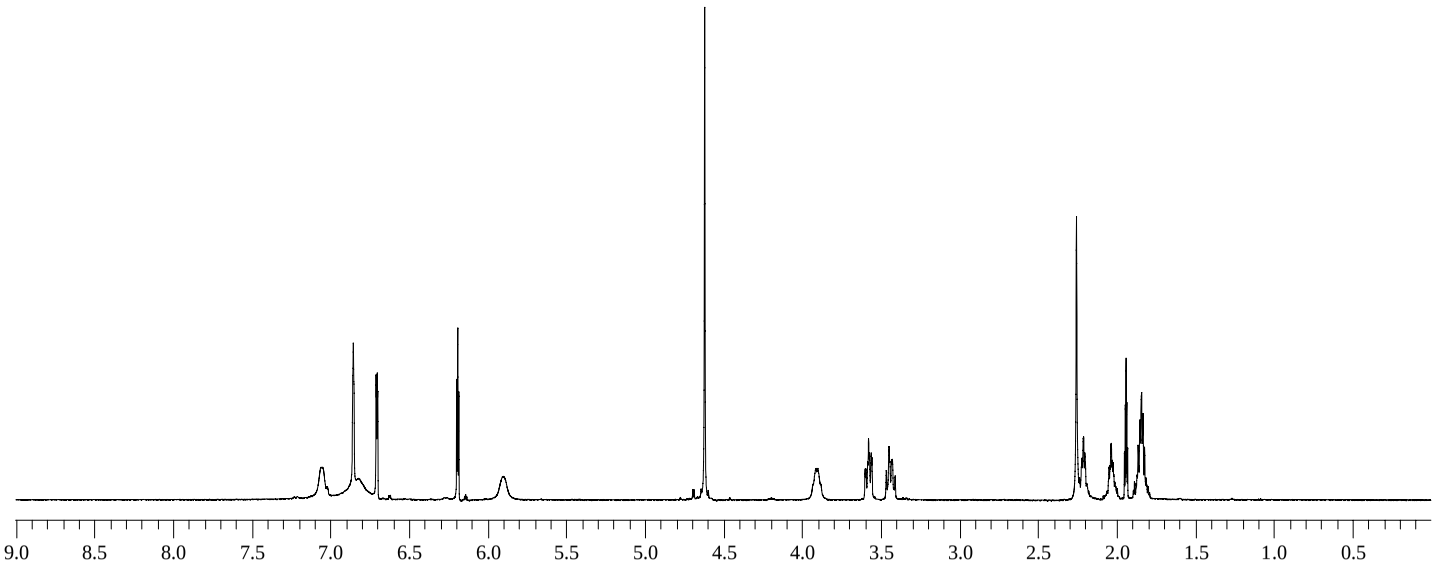


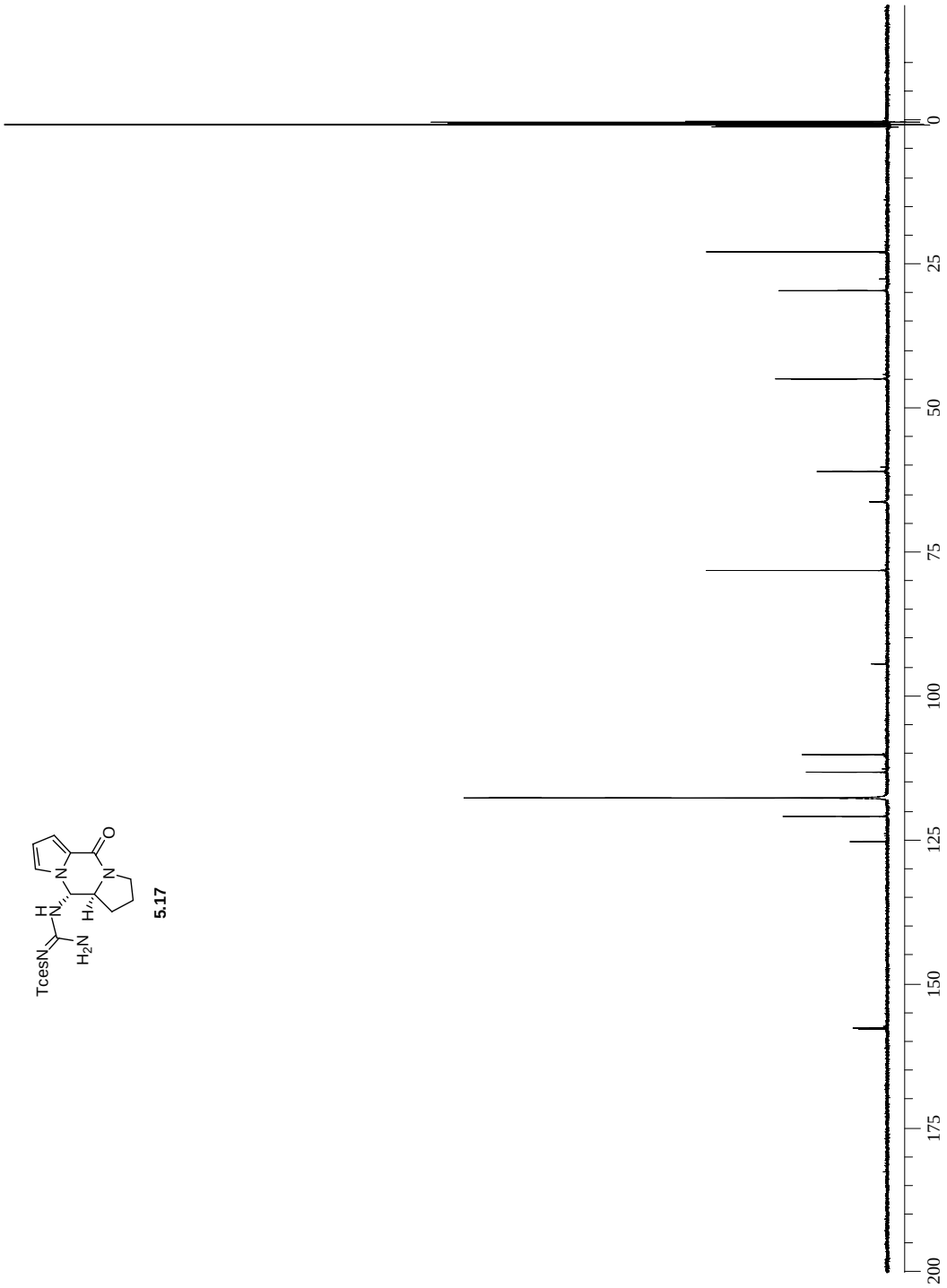
^{13}C-NMR spectrum of aminal **5.15** (in $CDCl_3$)



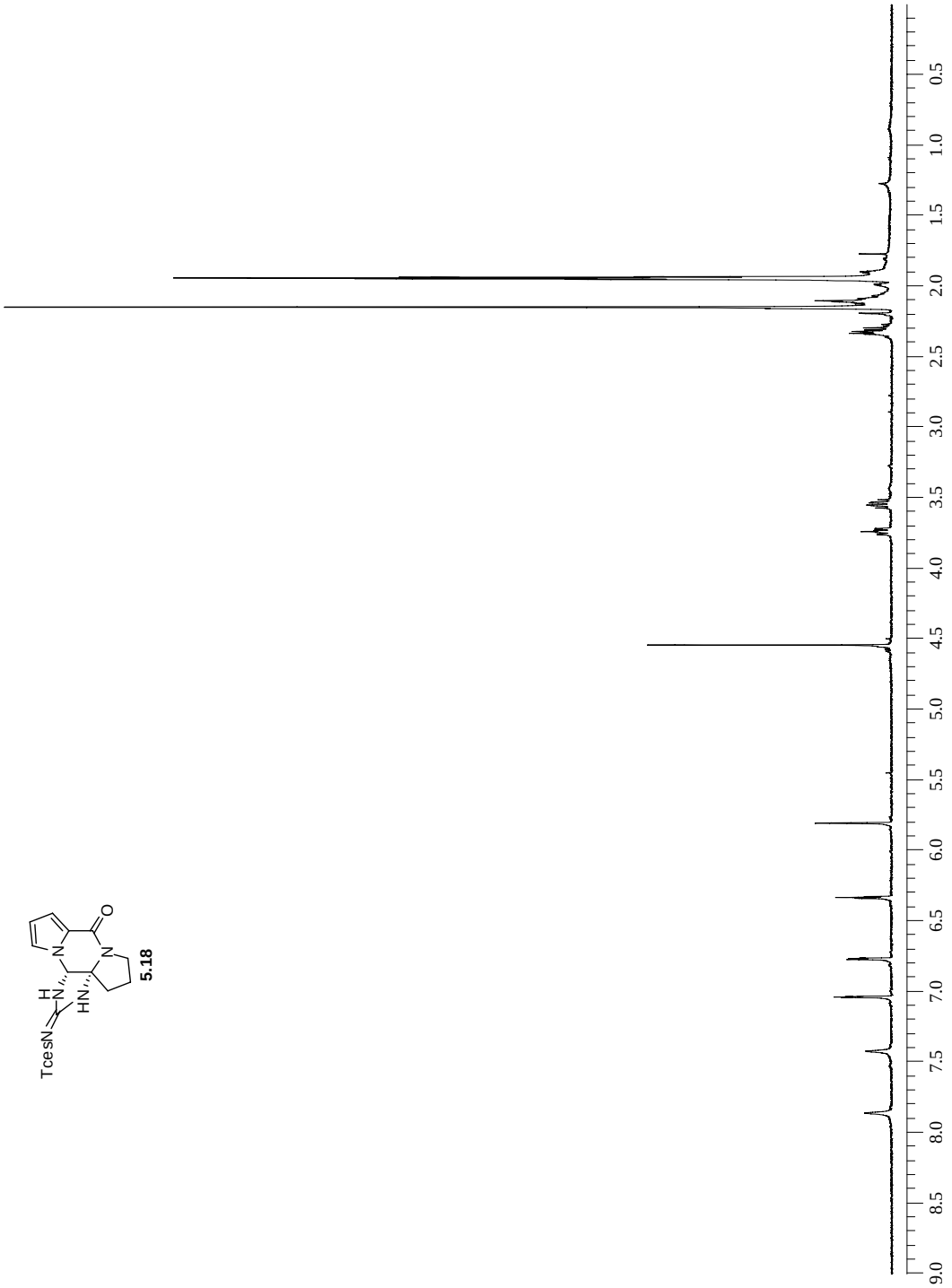
5.17



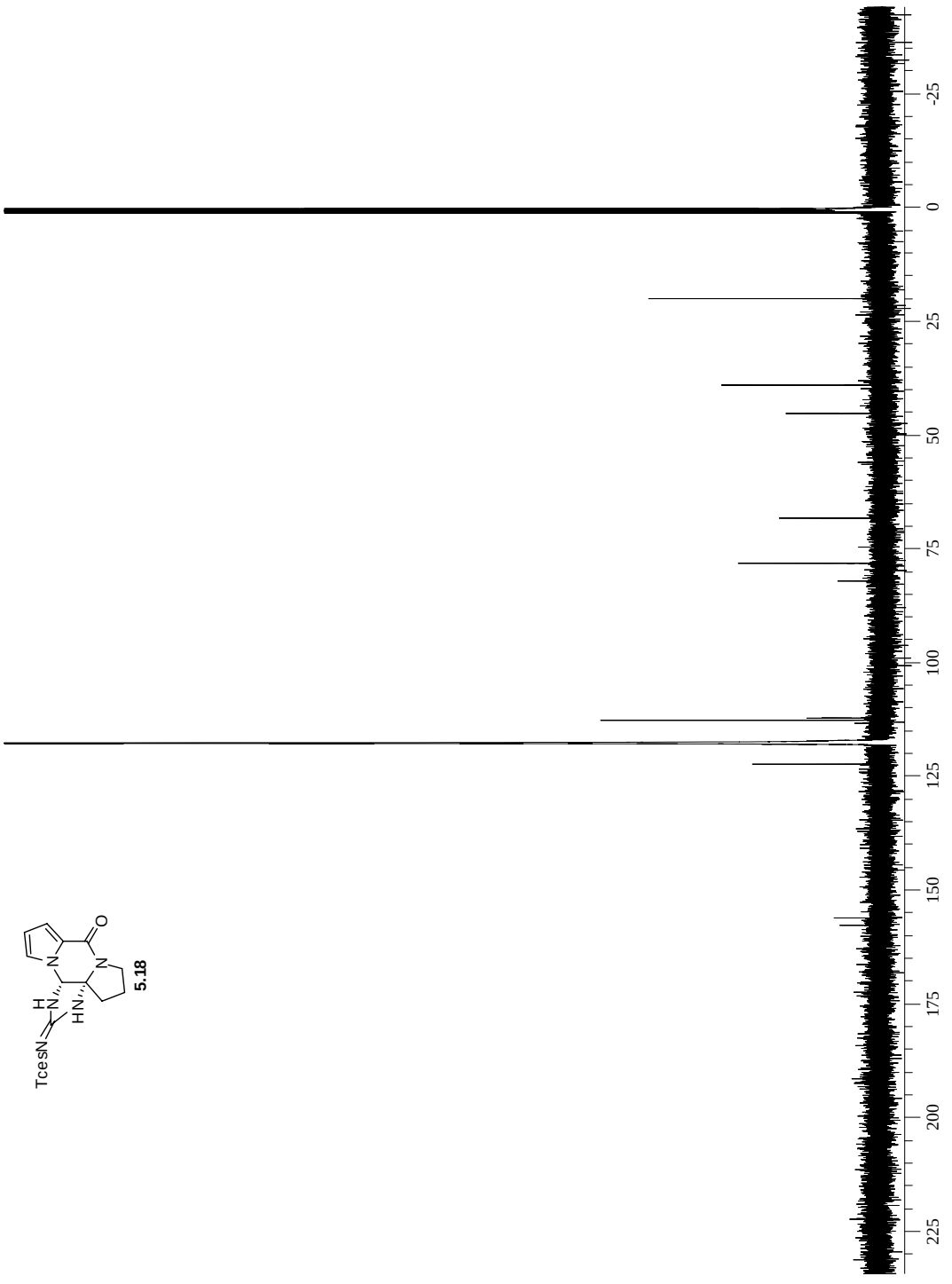
^{1}H-NMR spectrum of Tces-guanidine **5.17** (in CD_3CN)



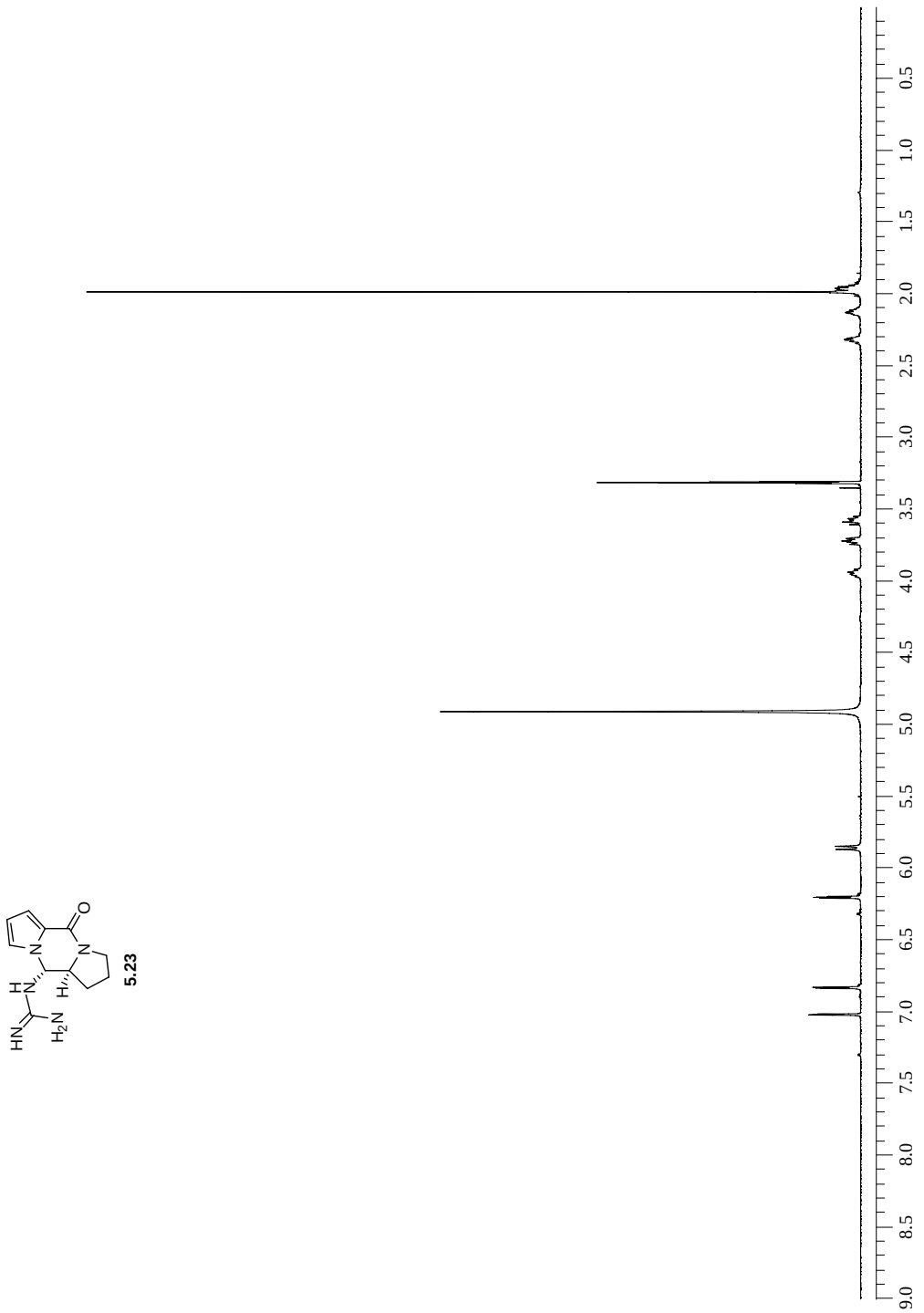
^{13}C-NMR spectrum of Tces-guanidine **5.17** (in CD_3CN)



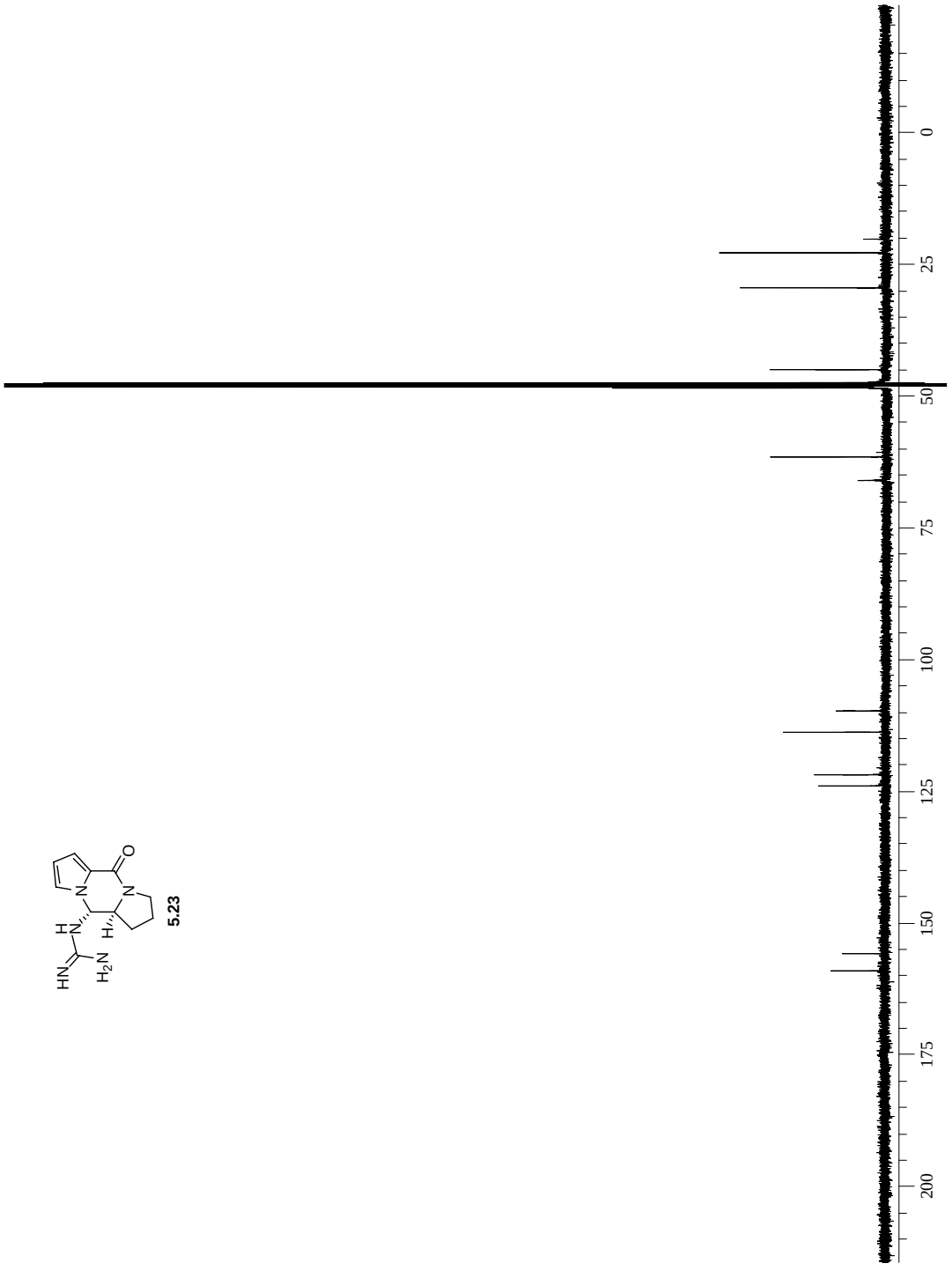
^{1}H-NMR spectrum of Tces-protected phakellin **5.18** (in CD_3CN)



^{13}C-NMR spectrum of Tces-protected phakellin **5.18** (in CD_3CN)

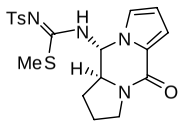


^{1}H-NMR spectrum of guanidine **5.23** (in CD_3OD)

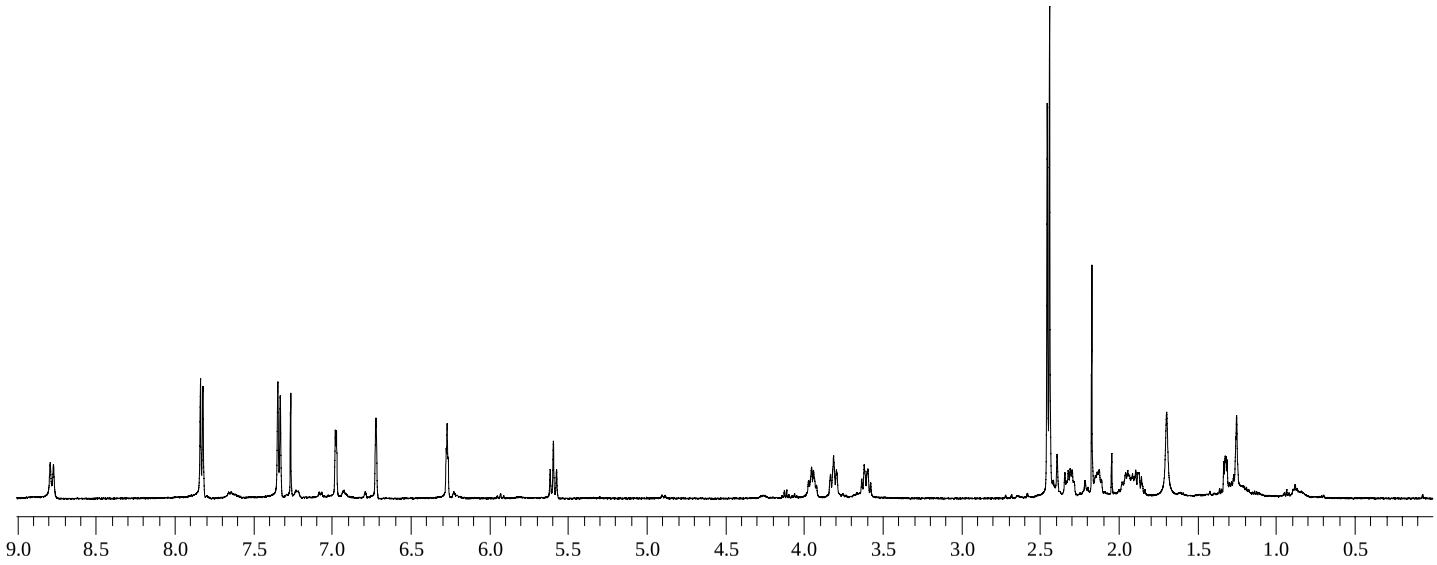


^{13}C-NMR spectrum of guanidine **5.23** (in CD_3OD)

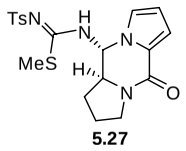
5.23



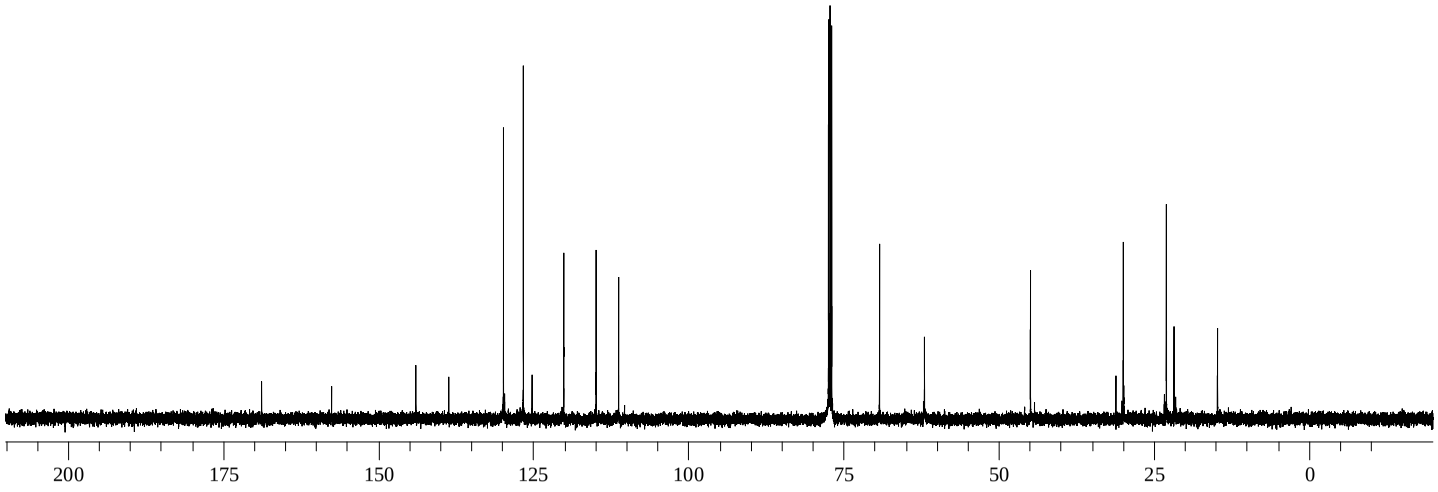
5.27



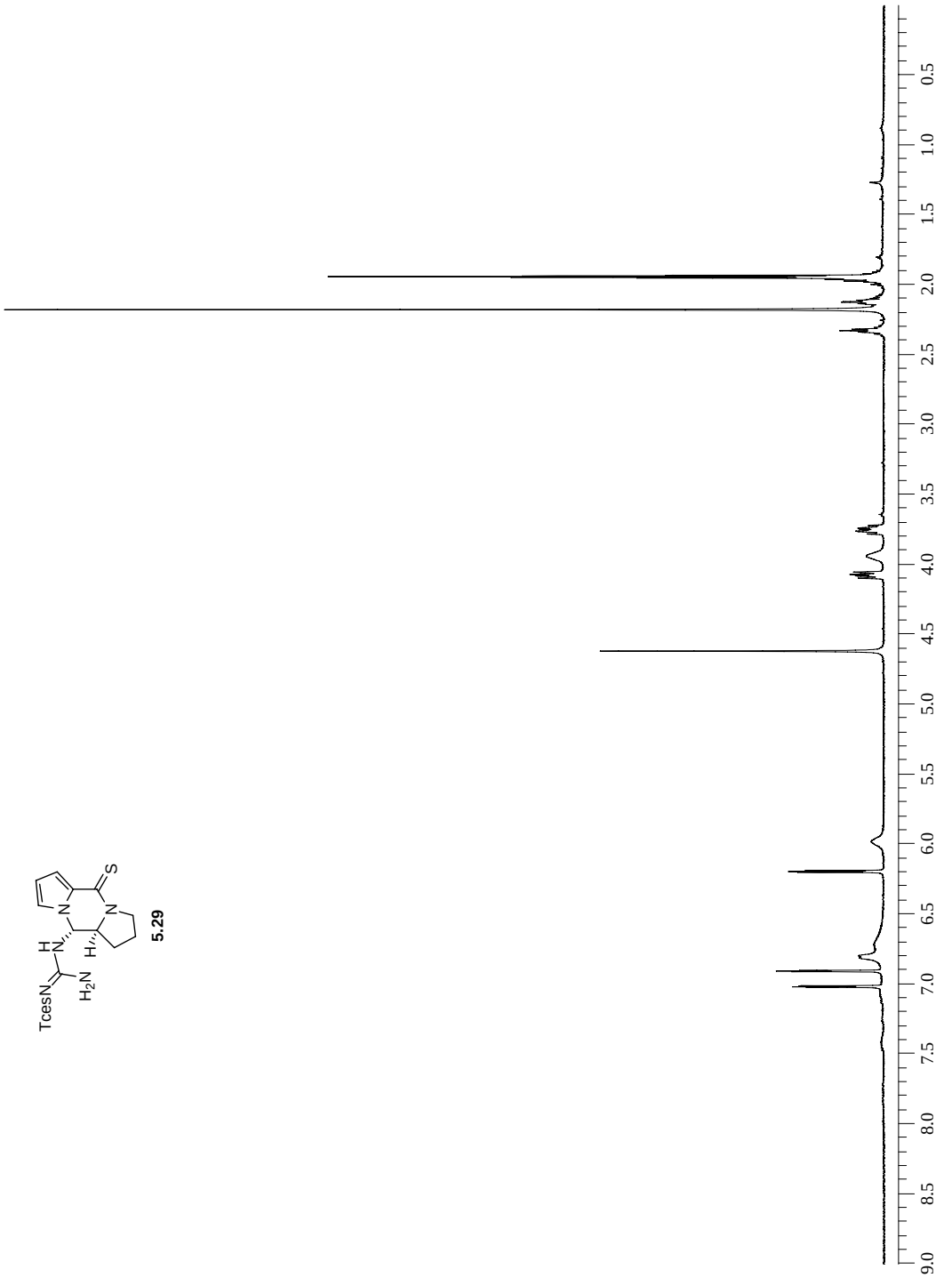
^{1}H-NMR spectrum of isothiourea **5.27** (in $CDCl_3$)



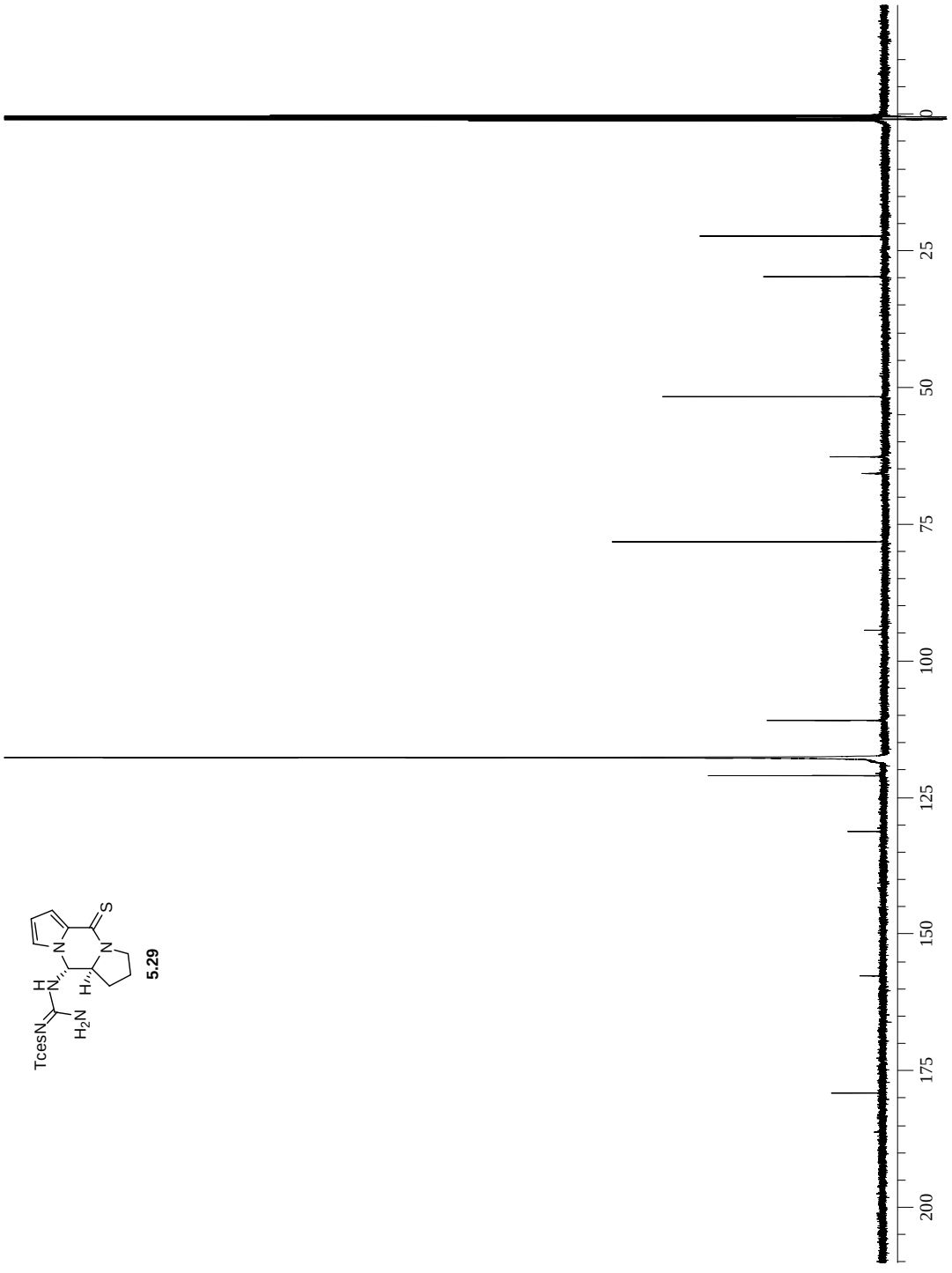
5.27



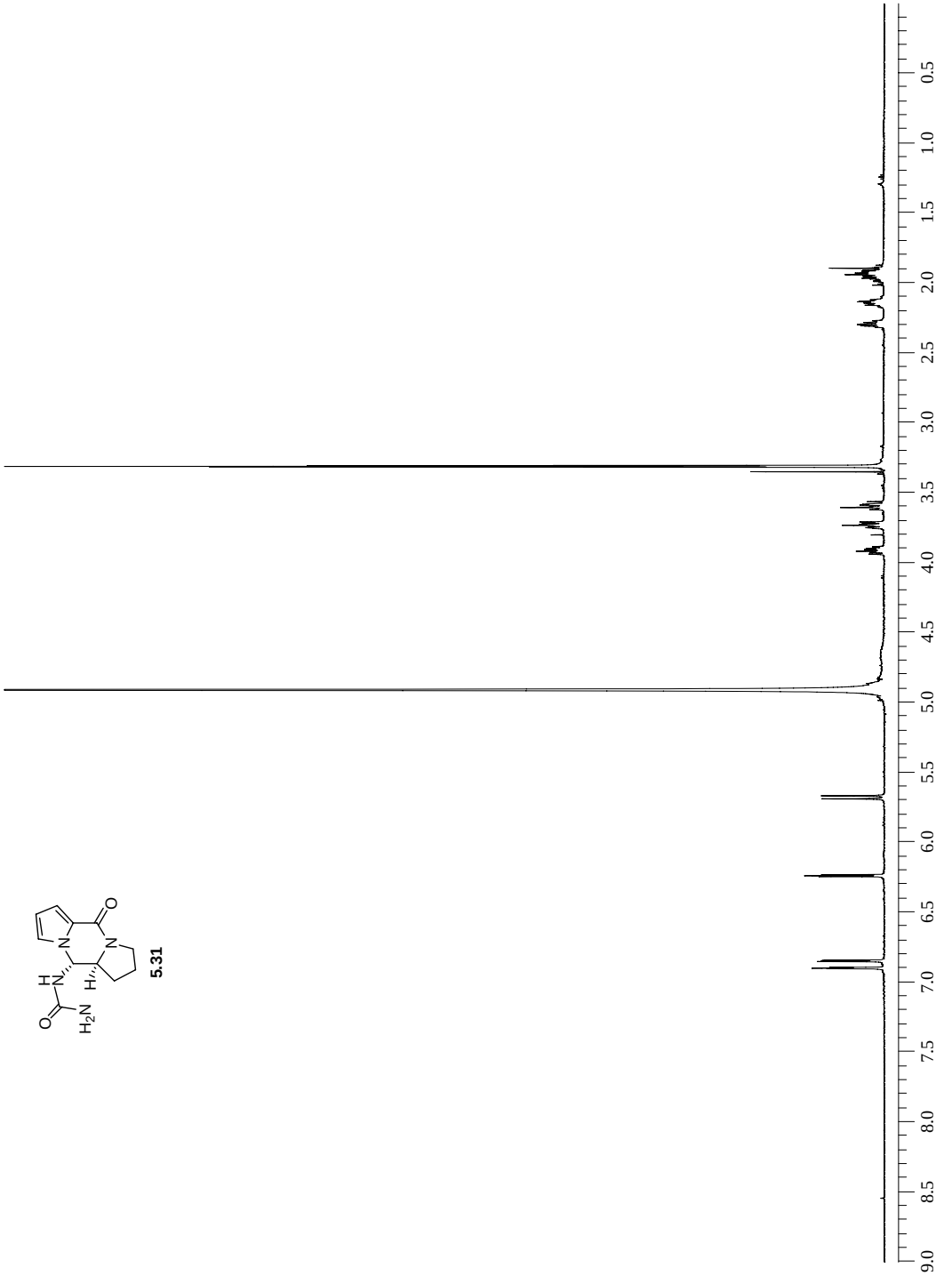
^{13}C-NMR spectrum of isothiourea **5.27** (in $CDCl_3$)



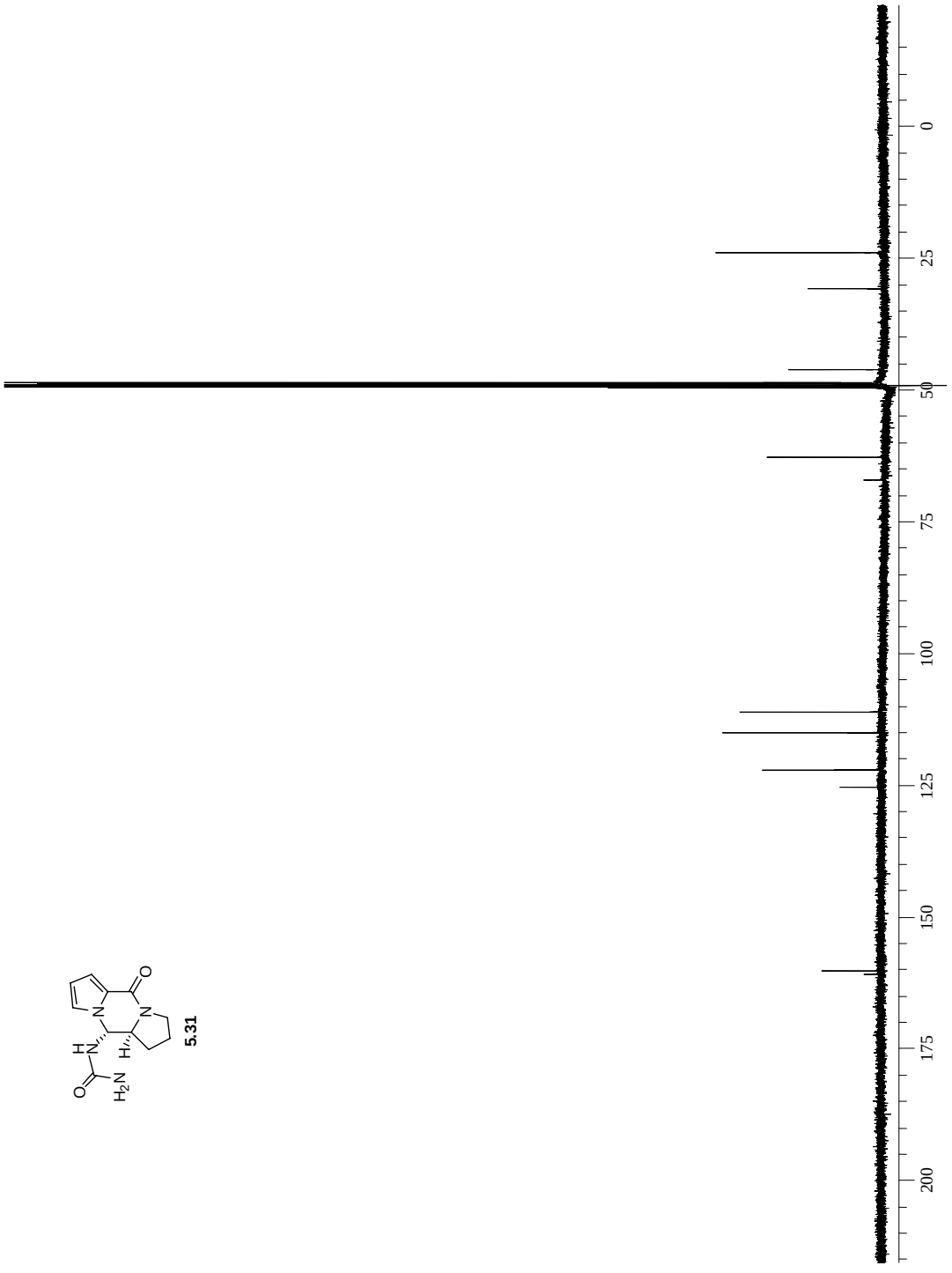
^{1}H-NMR spectrum of piperazine-thione **5.29** (in CD_3CN)



^{13}C-NMR spectrum of piperazine-thione **5.29** (in CD_3CN)

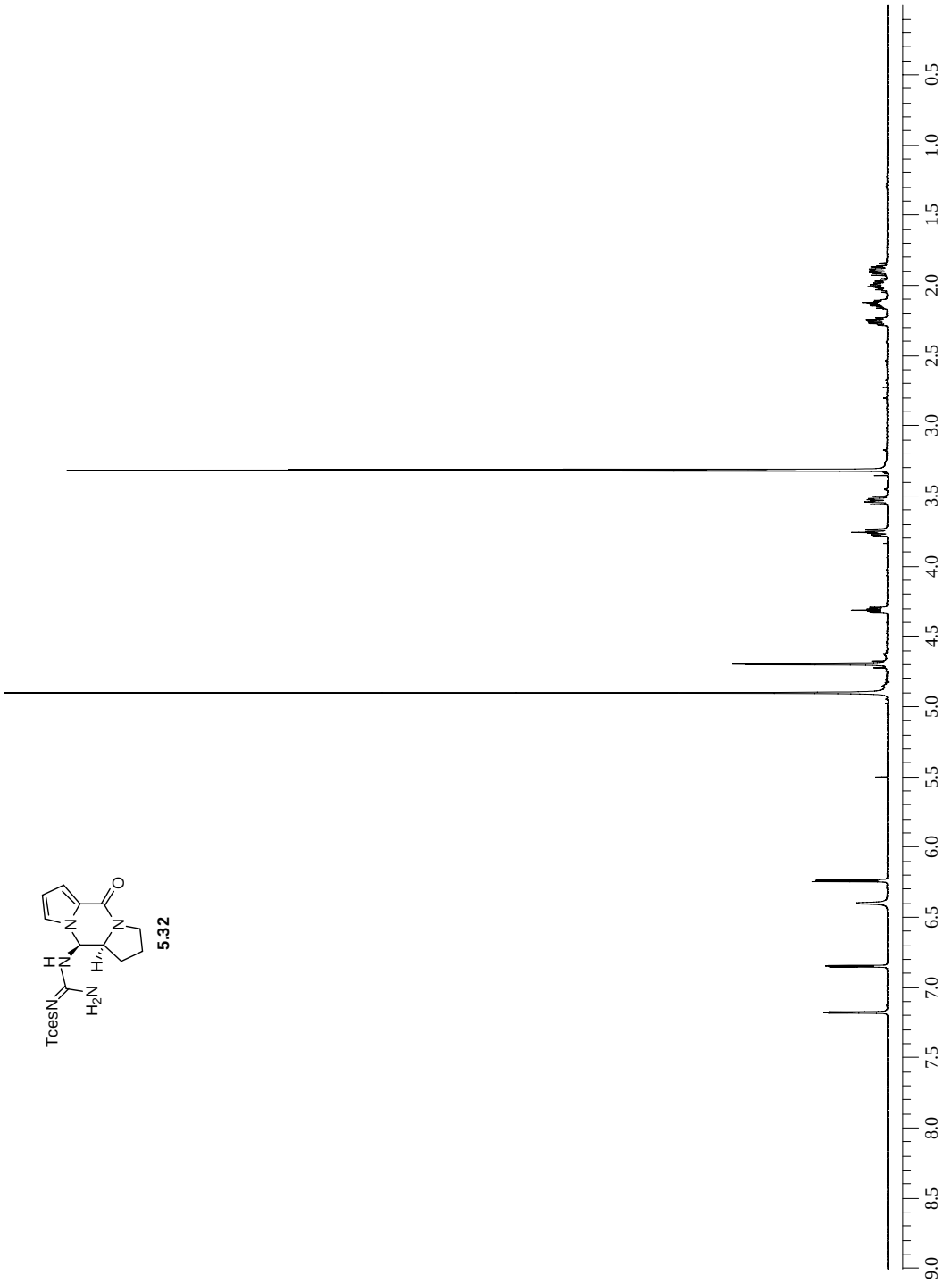


^{1}H-NMR spectrum of urea **5.31** (in CD_3OD)

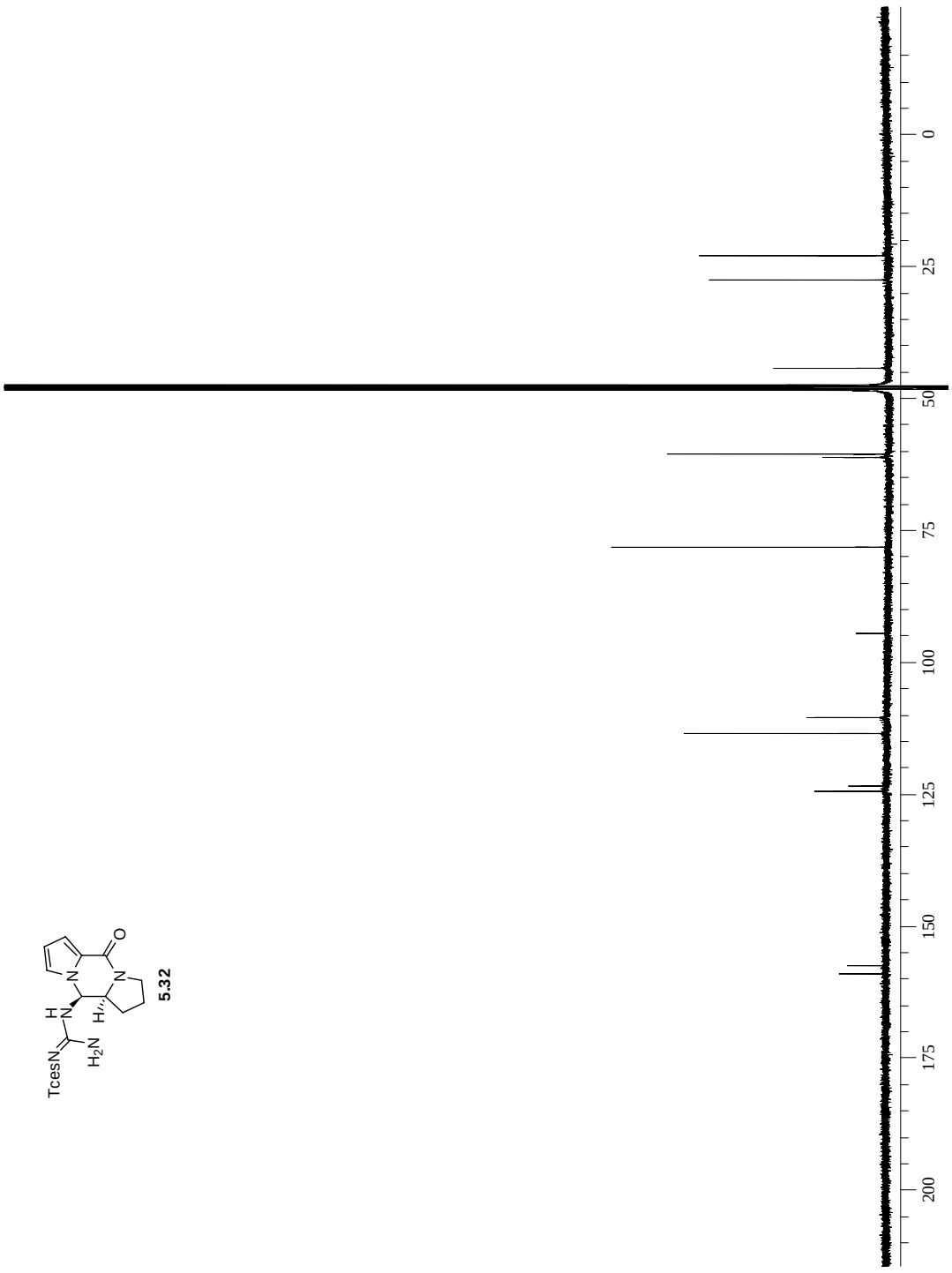


5.31

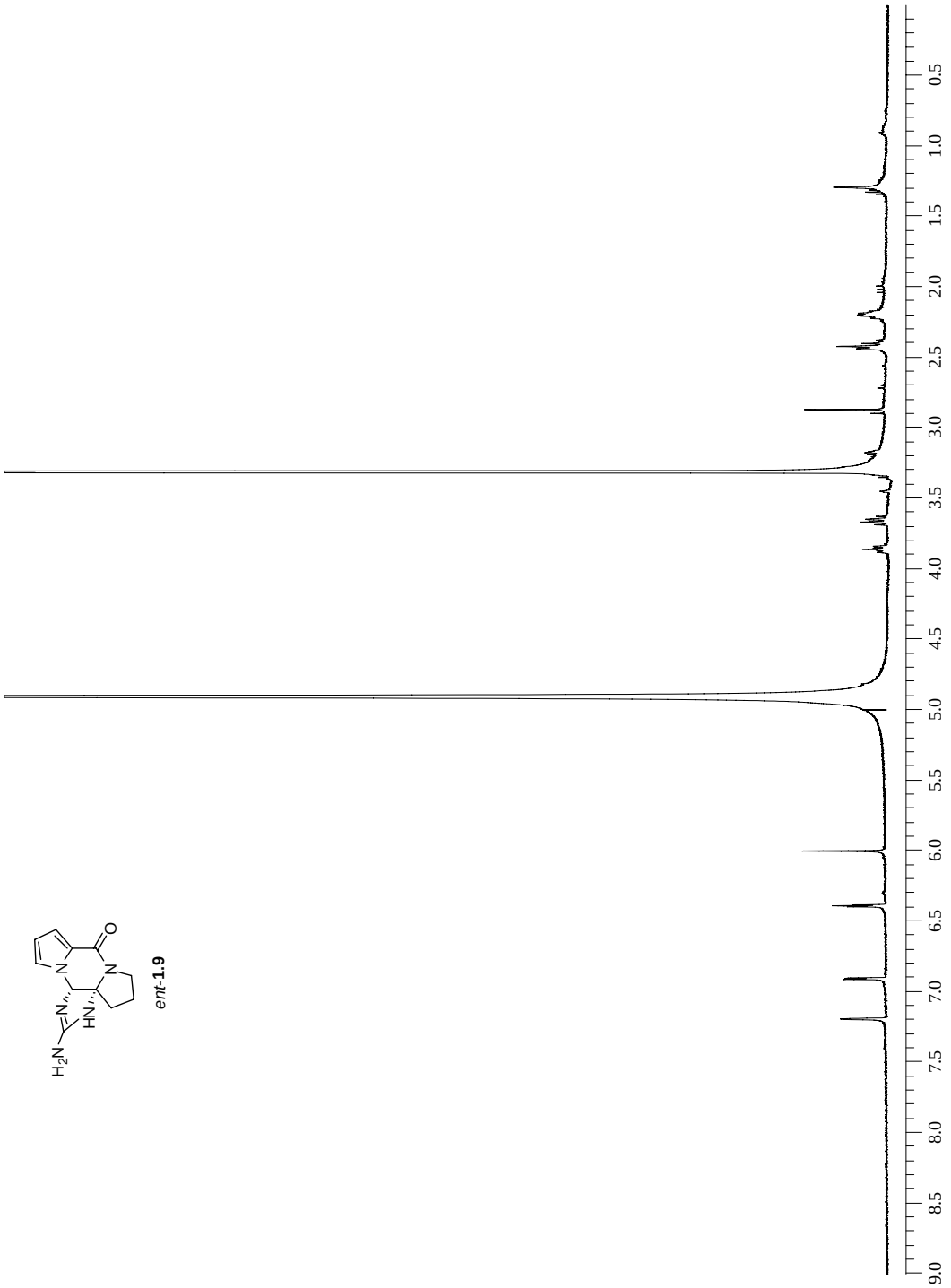
^{13}C-NMR spectrum of urea **5.31** (in CD_3OD)



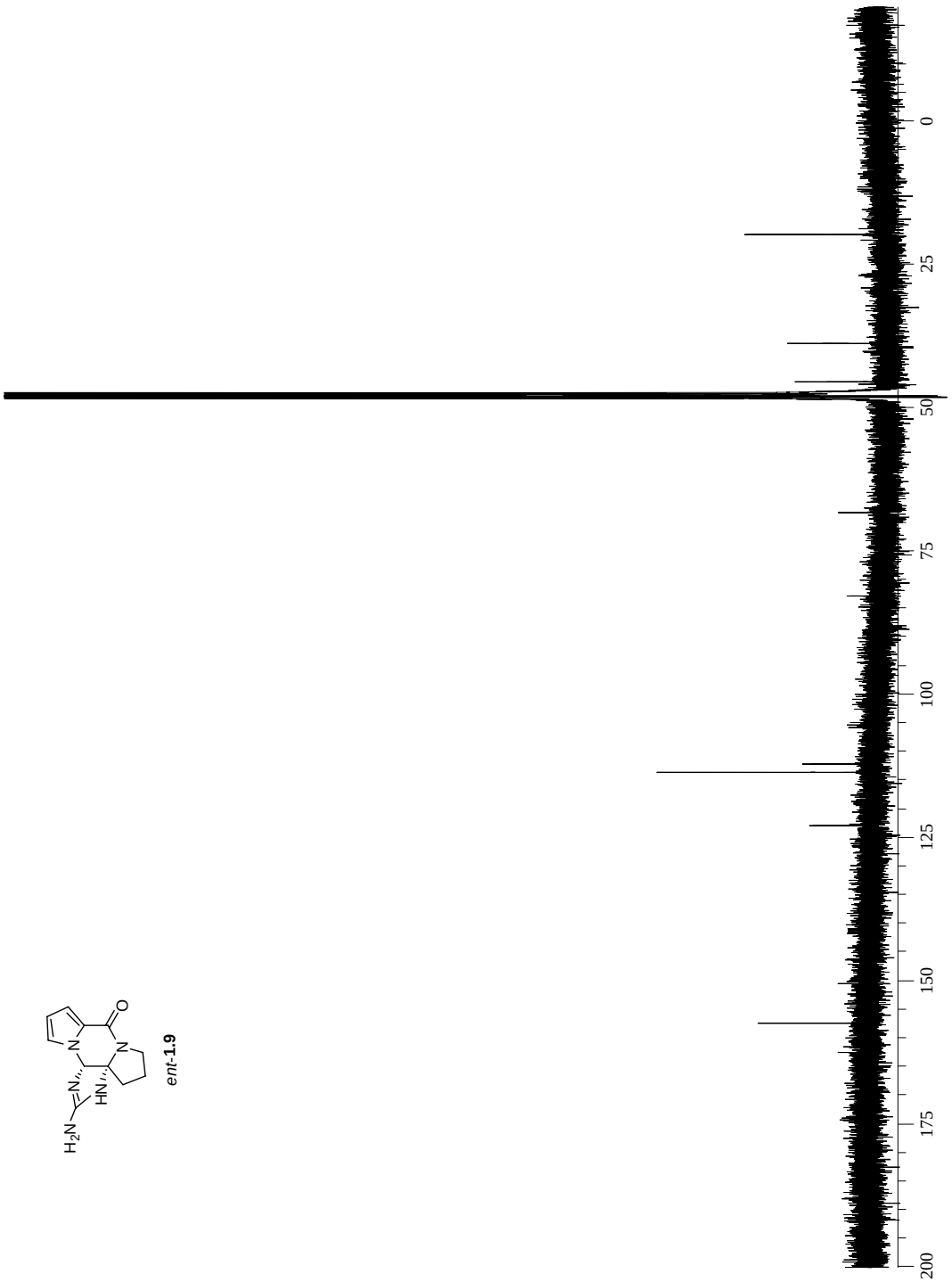
^{1}H-NMR spectrum of Tces-guanidine **5.32** (in CD_3OD)



^{13}C-NMR spectrum of Tces-guanidine **5.32** (in CD_3OD)

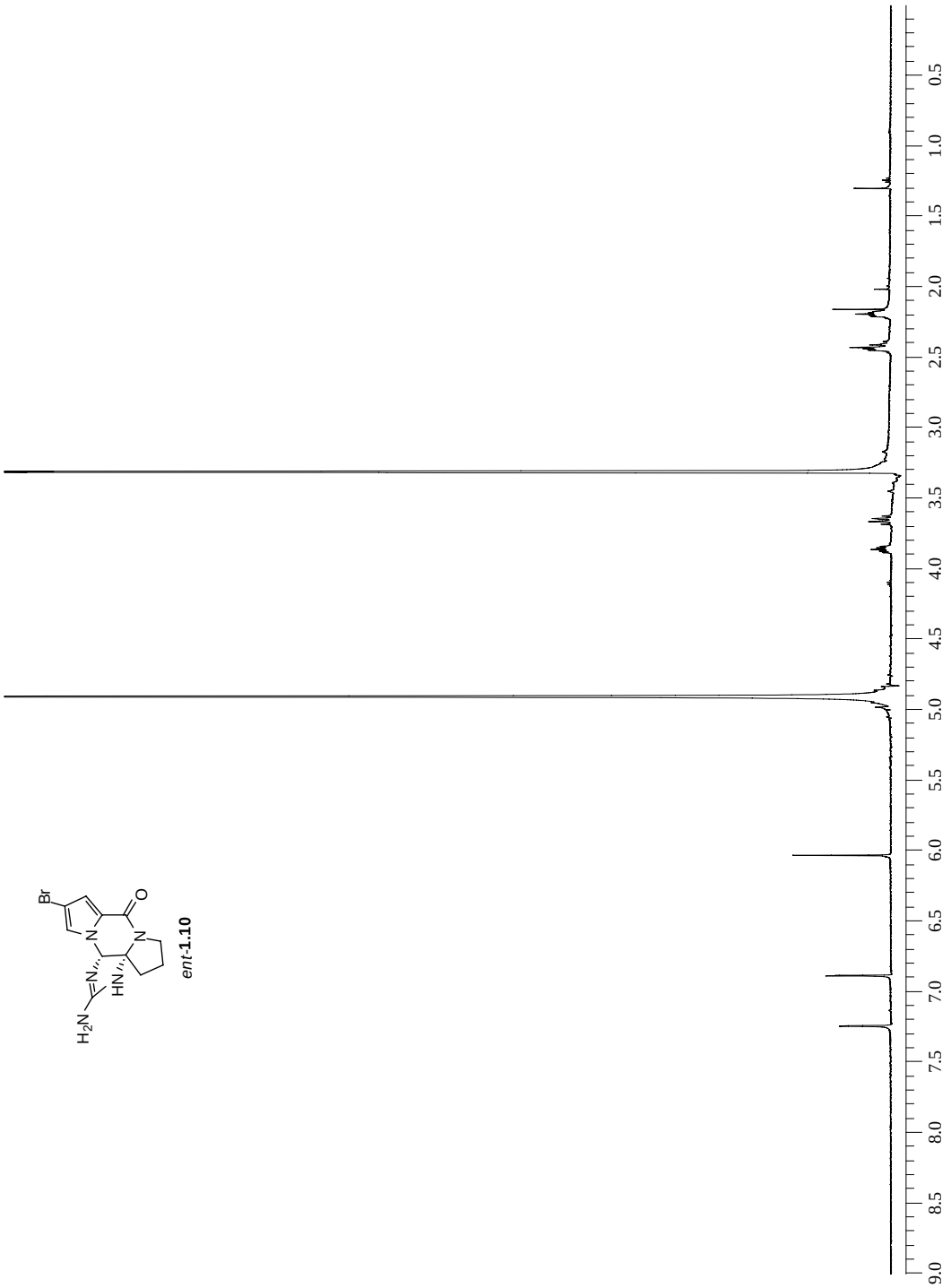


^{1}H-NMR spectrum of (+)-phakellin *ent*-**1.9** (in CD_3OD)

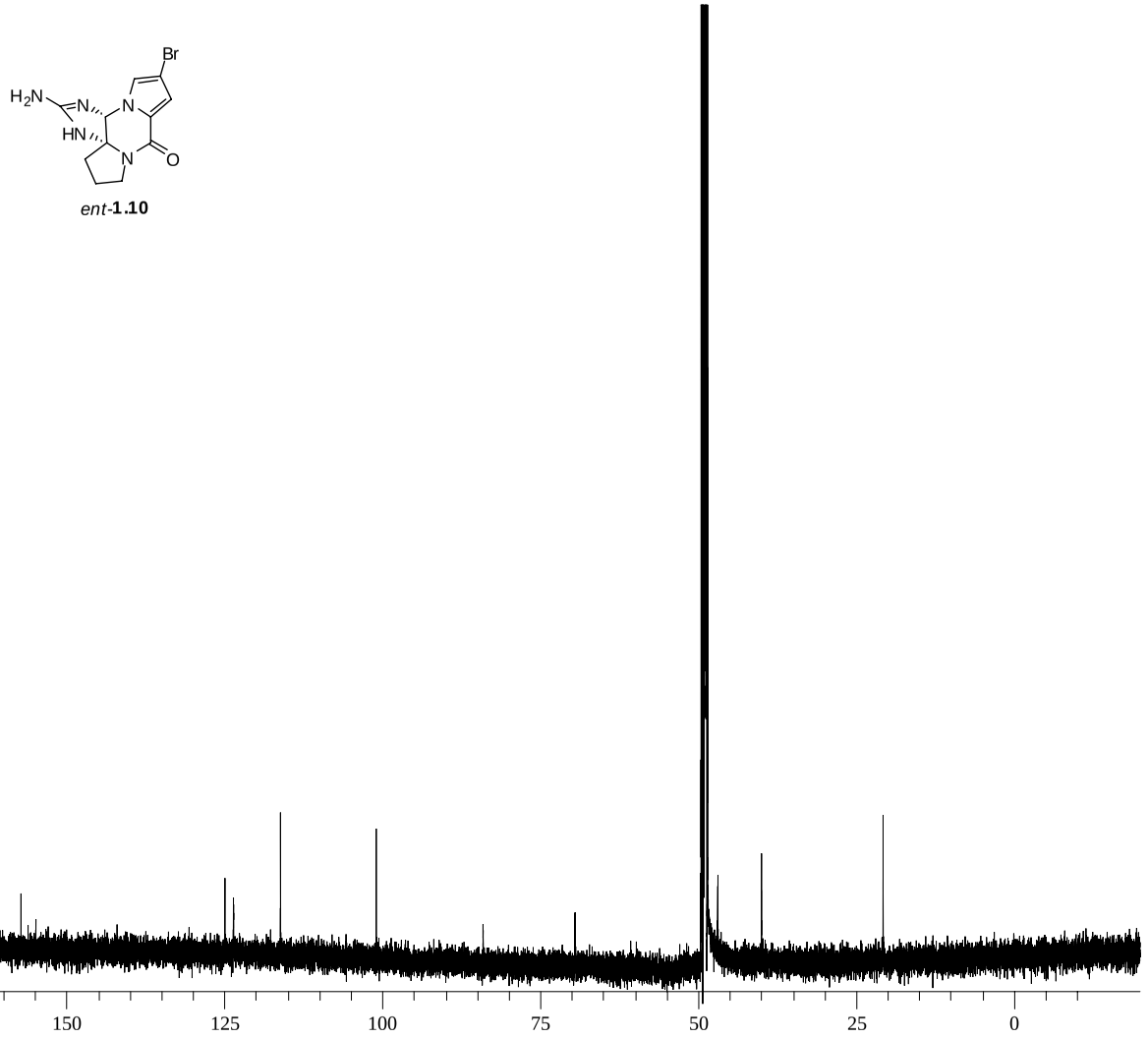


ent-**1.9**

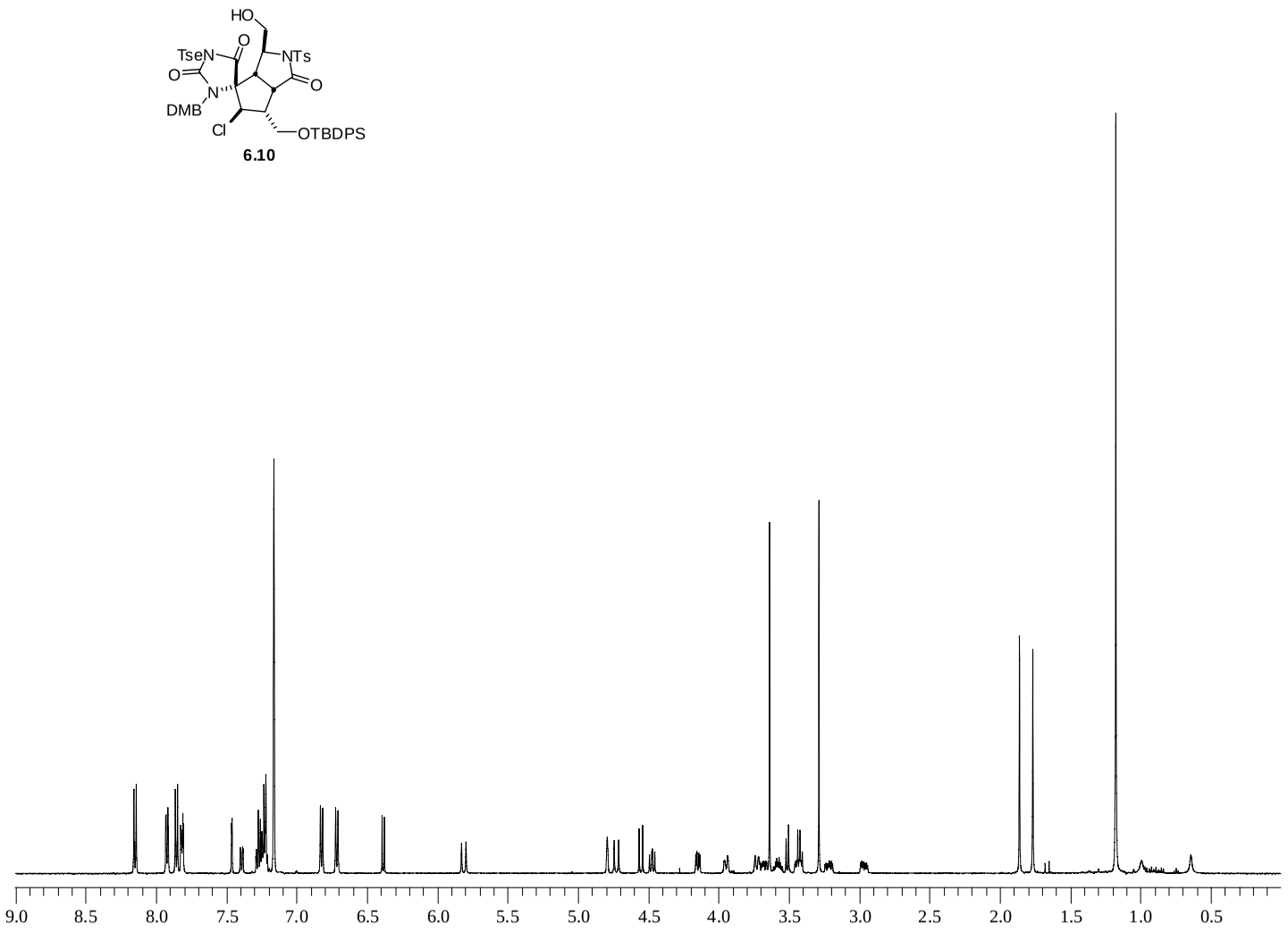
^{13}C-NMR spectrum of (+)-phakellin *ent*-**1.9** (in CD_3OD)



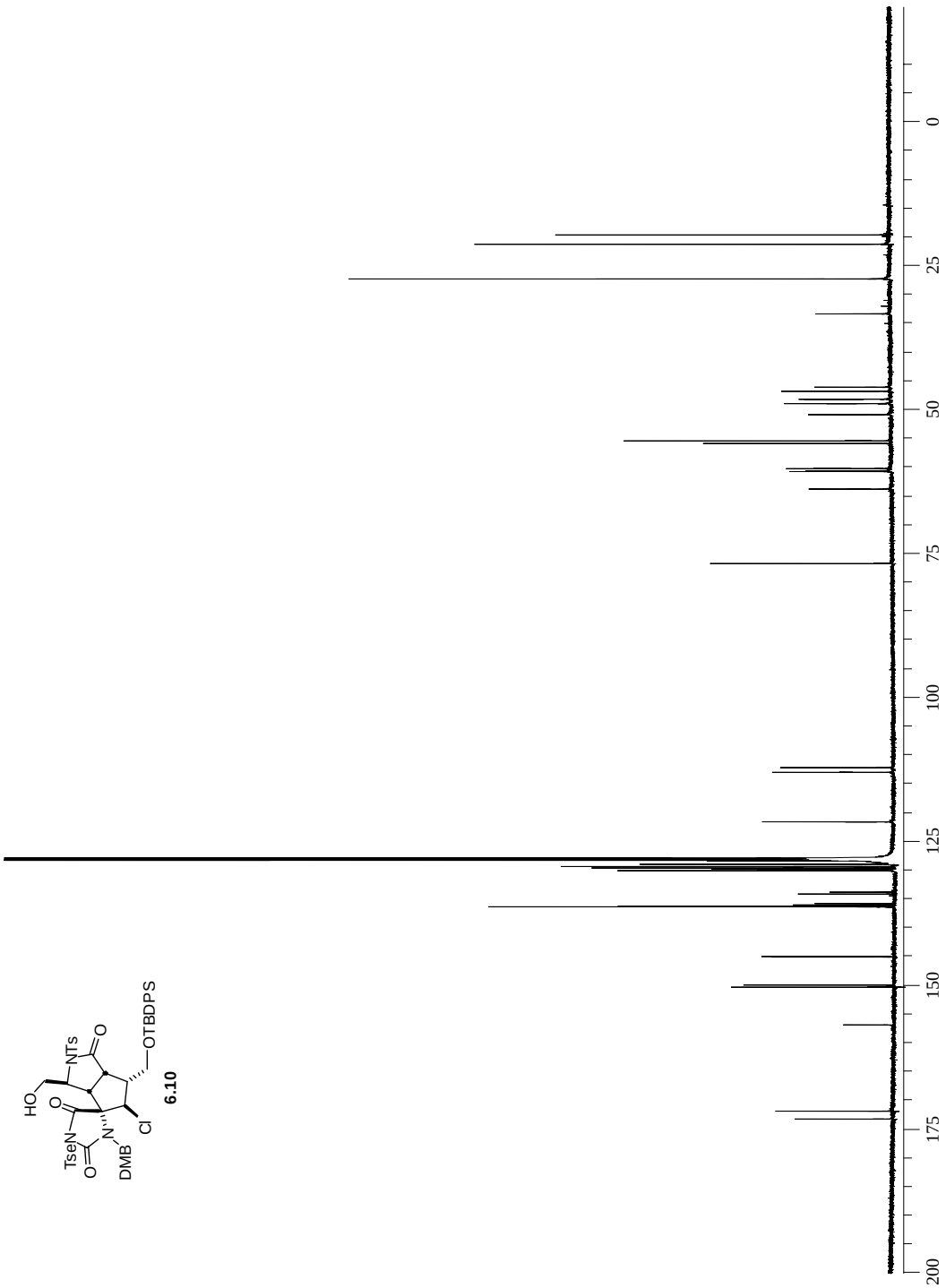
^{1}H-NMR spectrum of (+)-monobromophakellin *ent*-**1.10** (in CD_3OD)



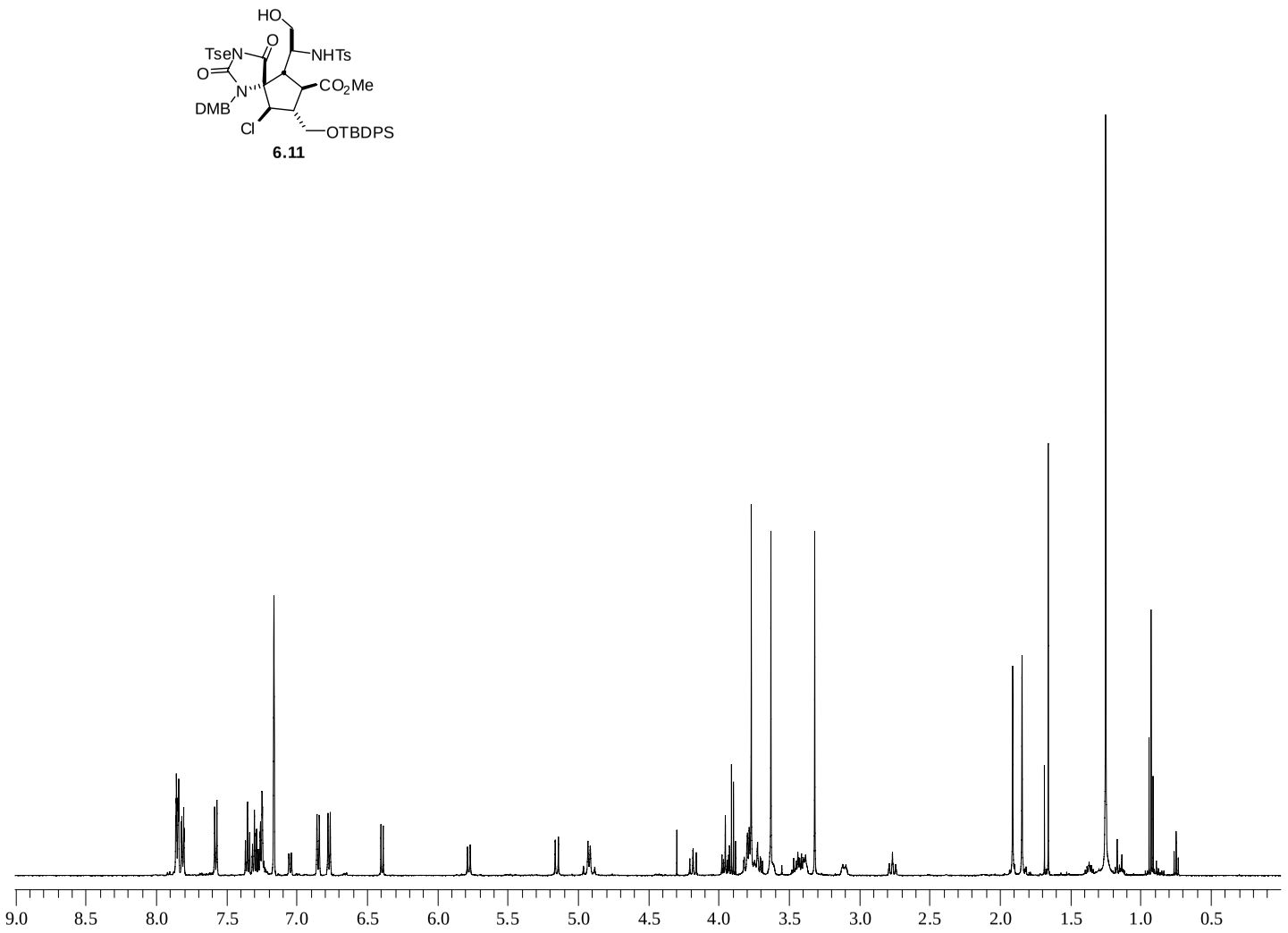
^{13}C-NMR spectrum of (+)-monobromophakellin *ent*-**1.10** (in CD_3OD)



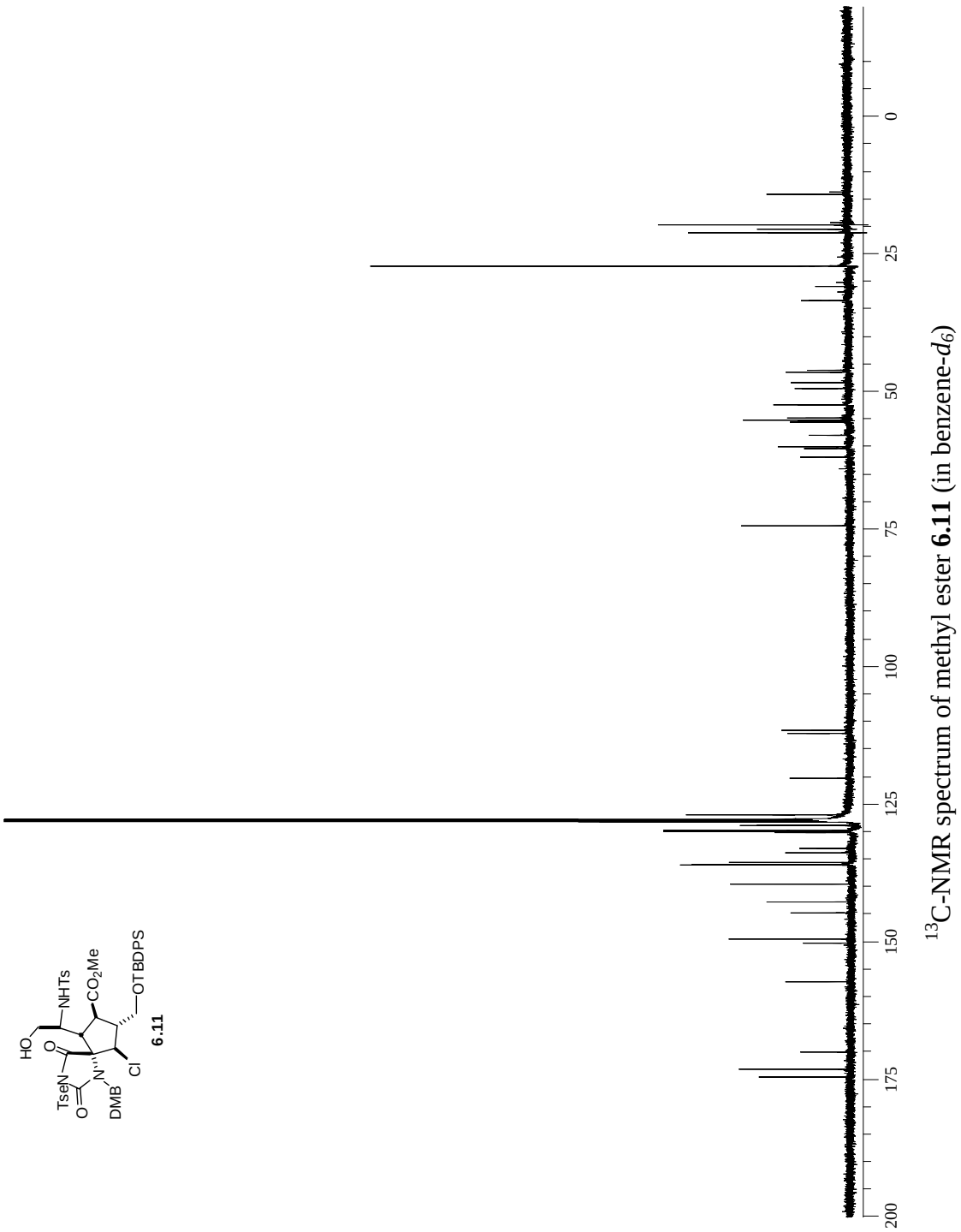
^{1}H-NMR spectrum of alcohol **6.10** (in benzene-d_6)



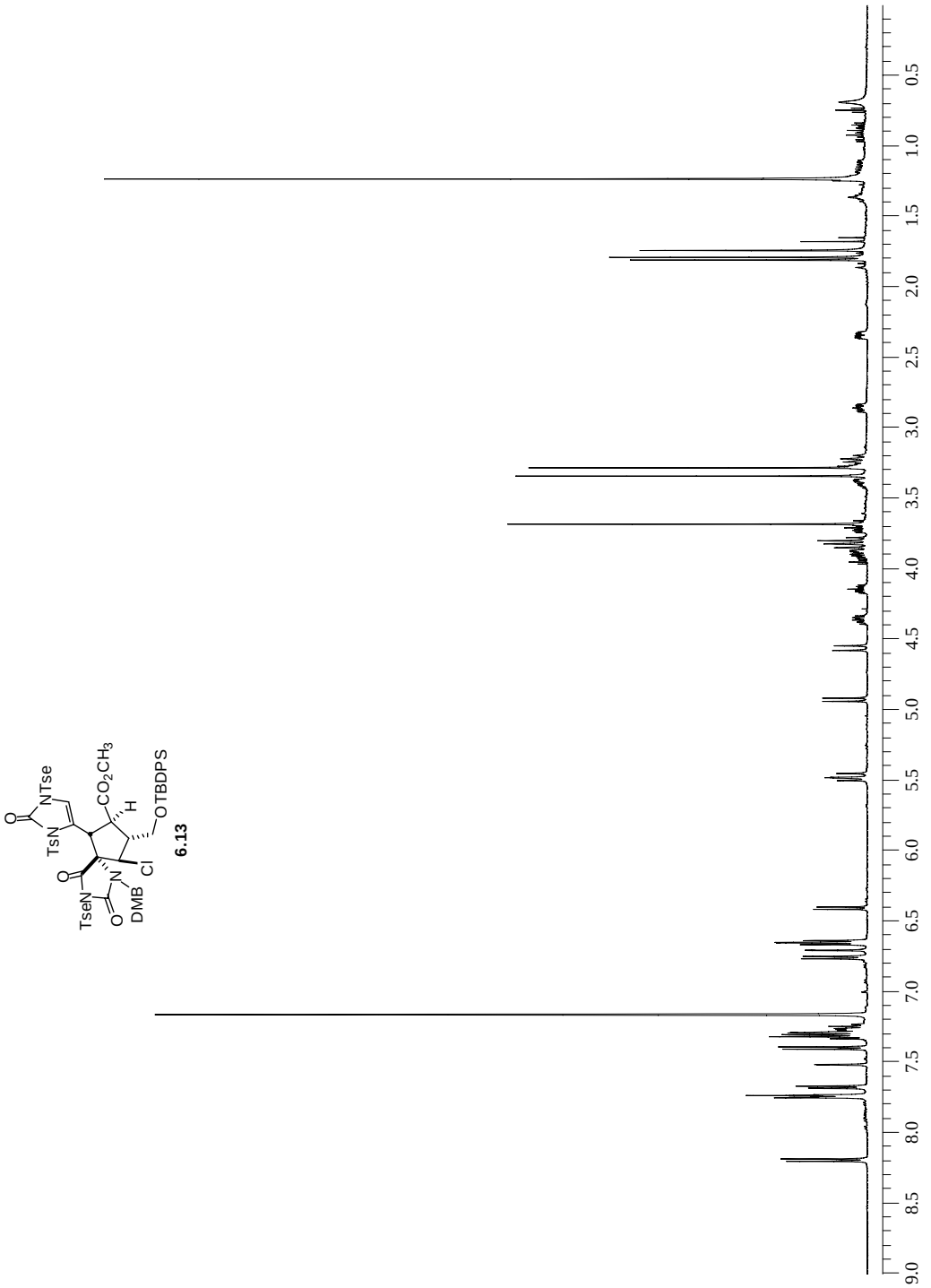
^{13}C-NMR spectrum of alcohol **6.10** (in benzene-d_6)



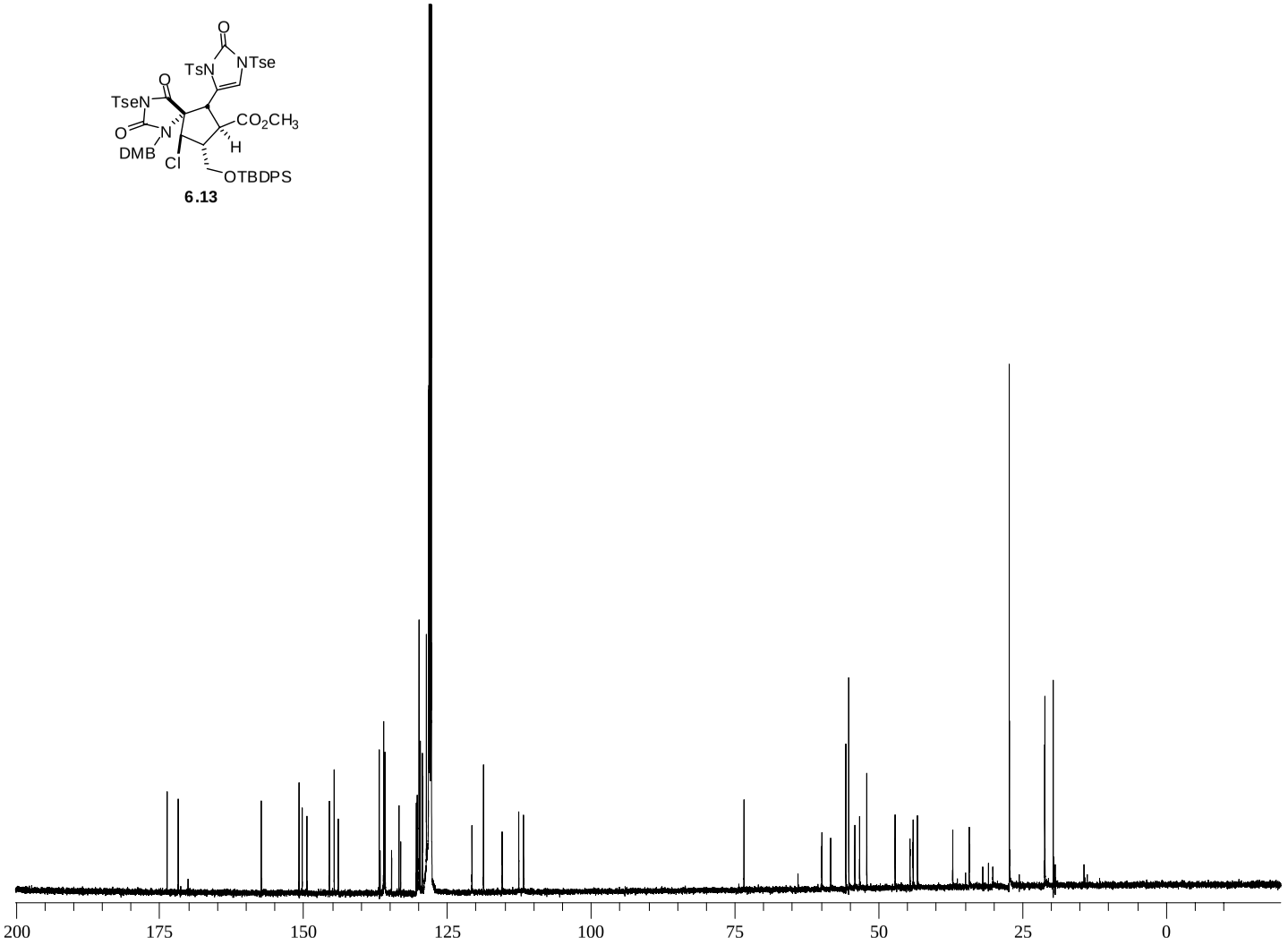
^{1}H-NMR spectrum of methyl ester **6.11** (in benzene-d_6)



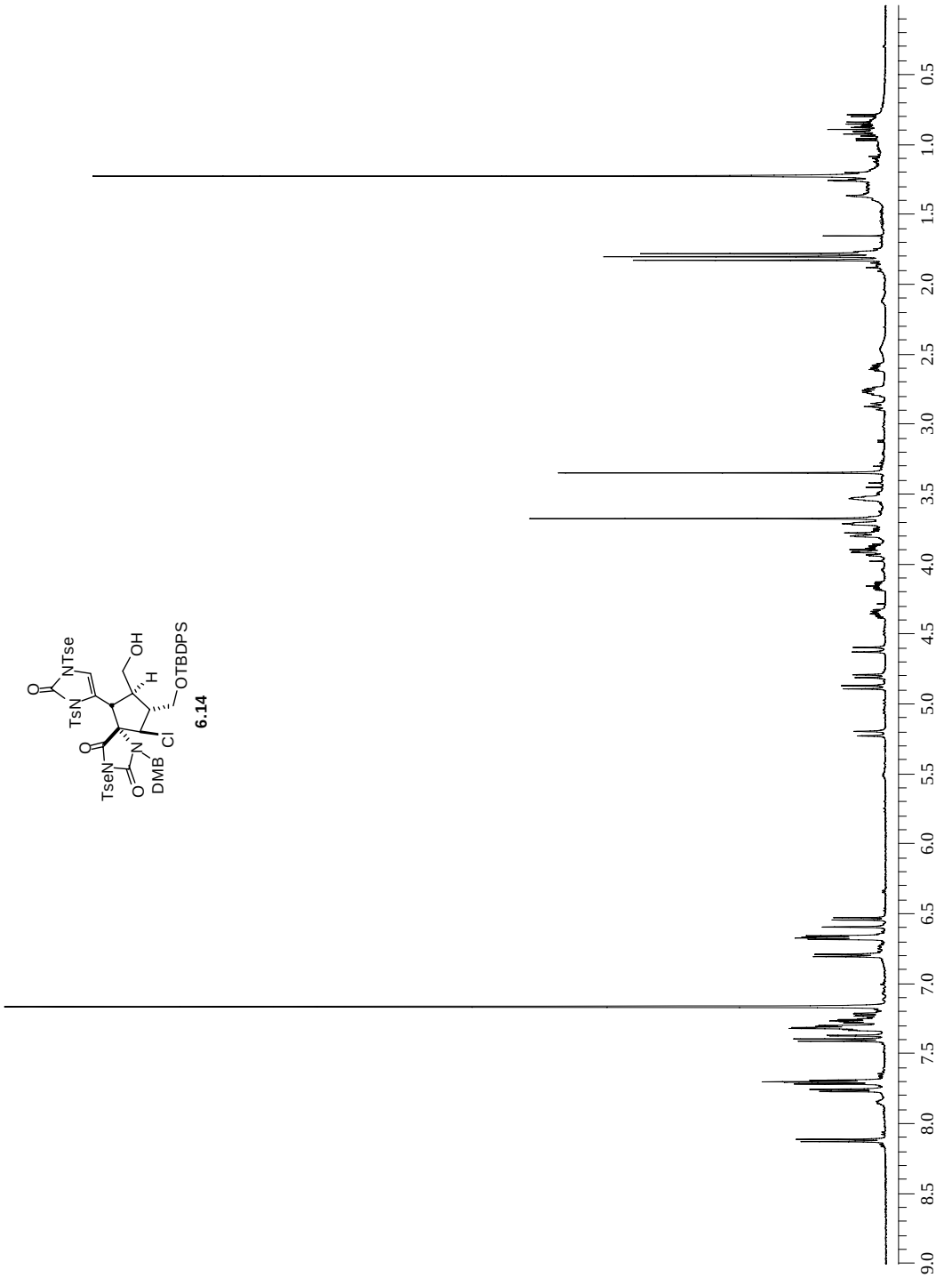
^{13}C-NMR spectrum of methyl ester **6.11** (in benzene-d_6)



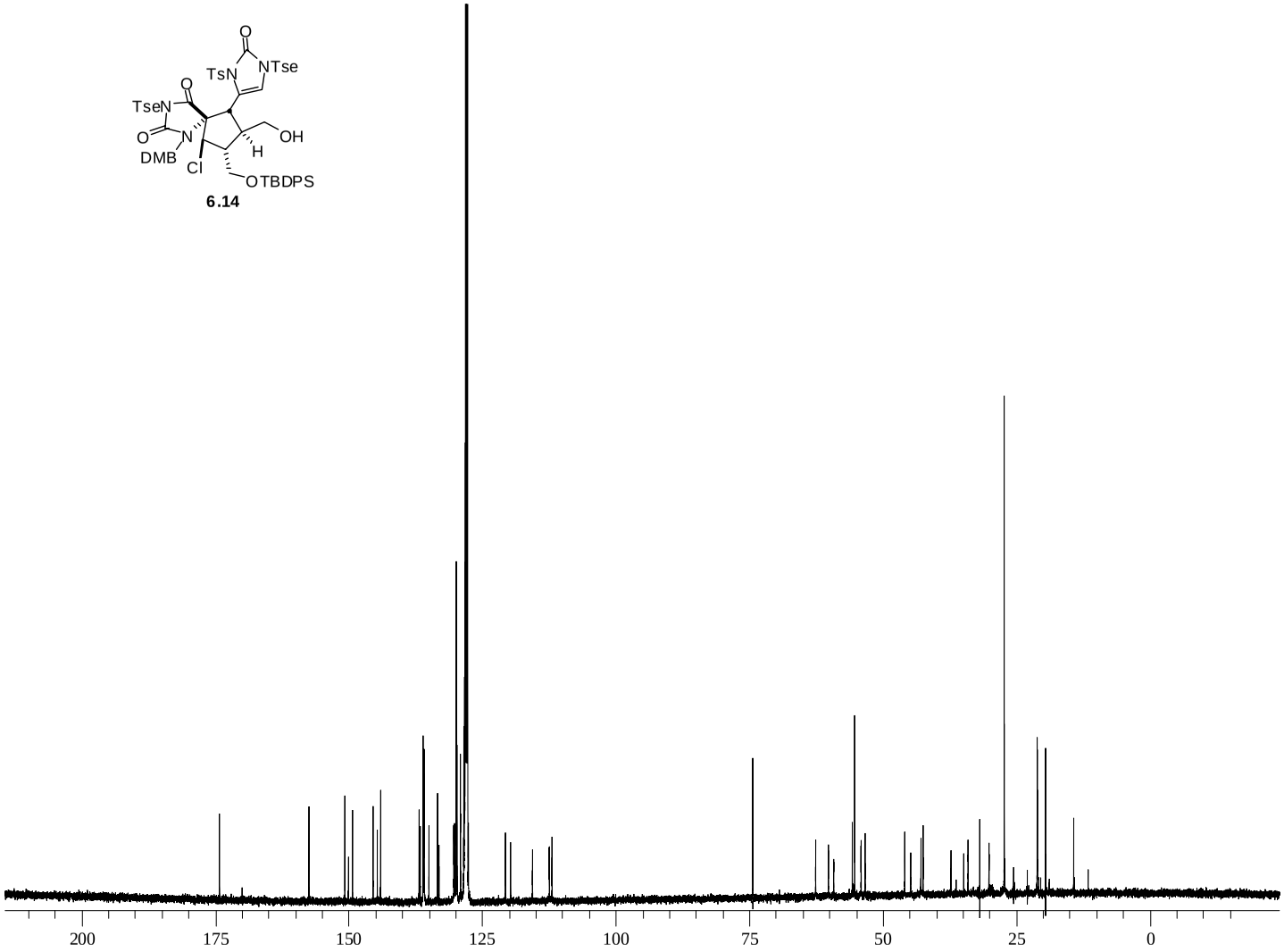
^{1}H-NMR spectrum of imidazolone **6.13** (in benzene-d_6)



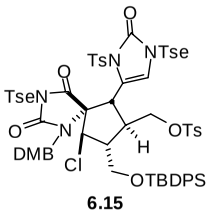
^{13}C-NMR spectrum of imidazolone **6.13** (in benzene-d_6)



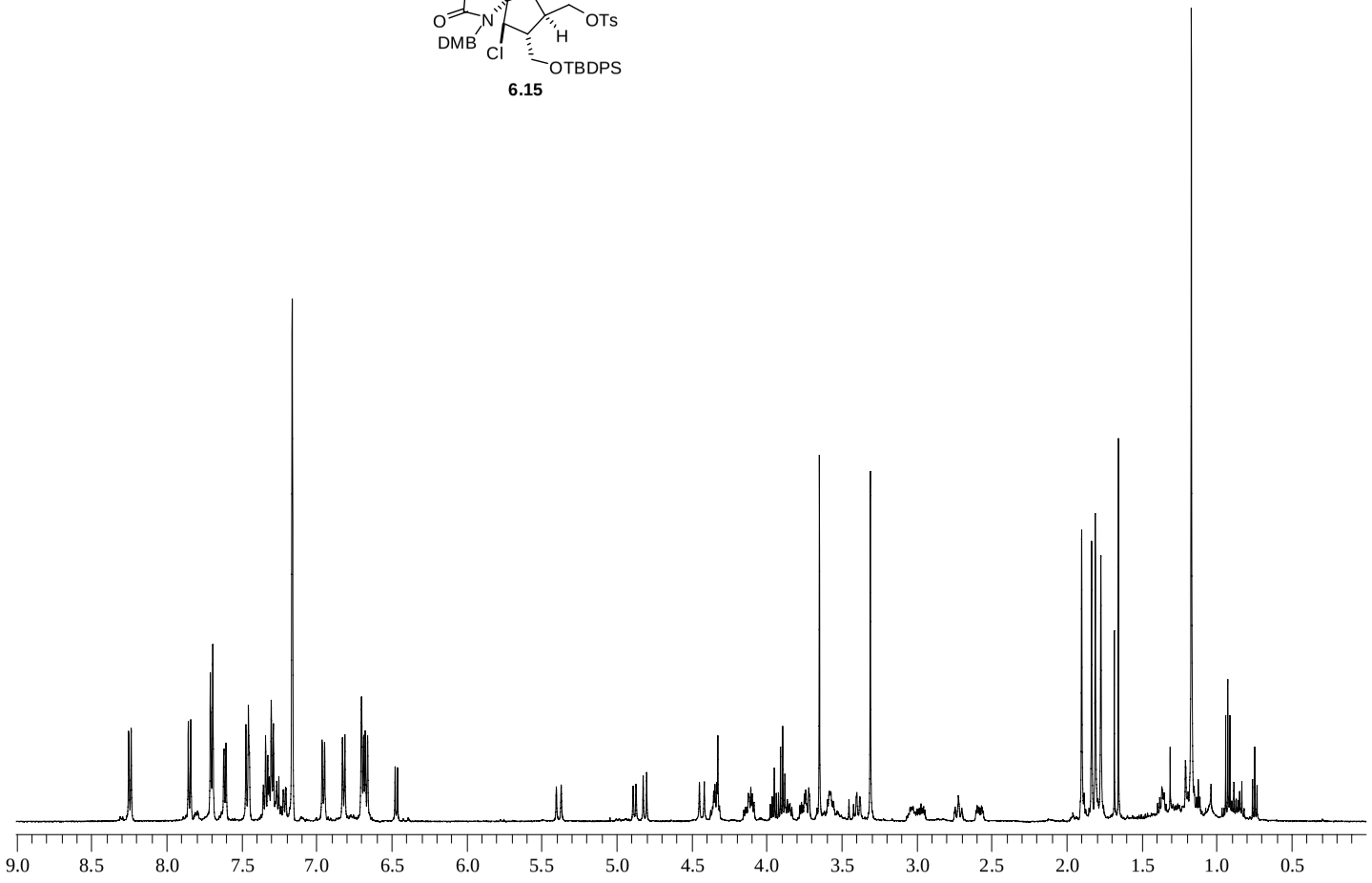
^{1}H-NMR spectrum of alcohol **6.14** (in benzene-d_6)



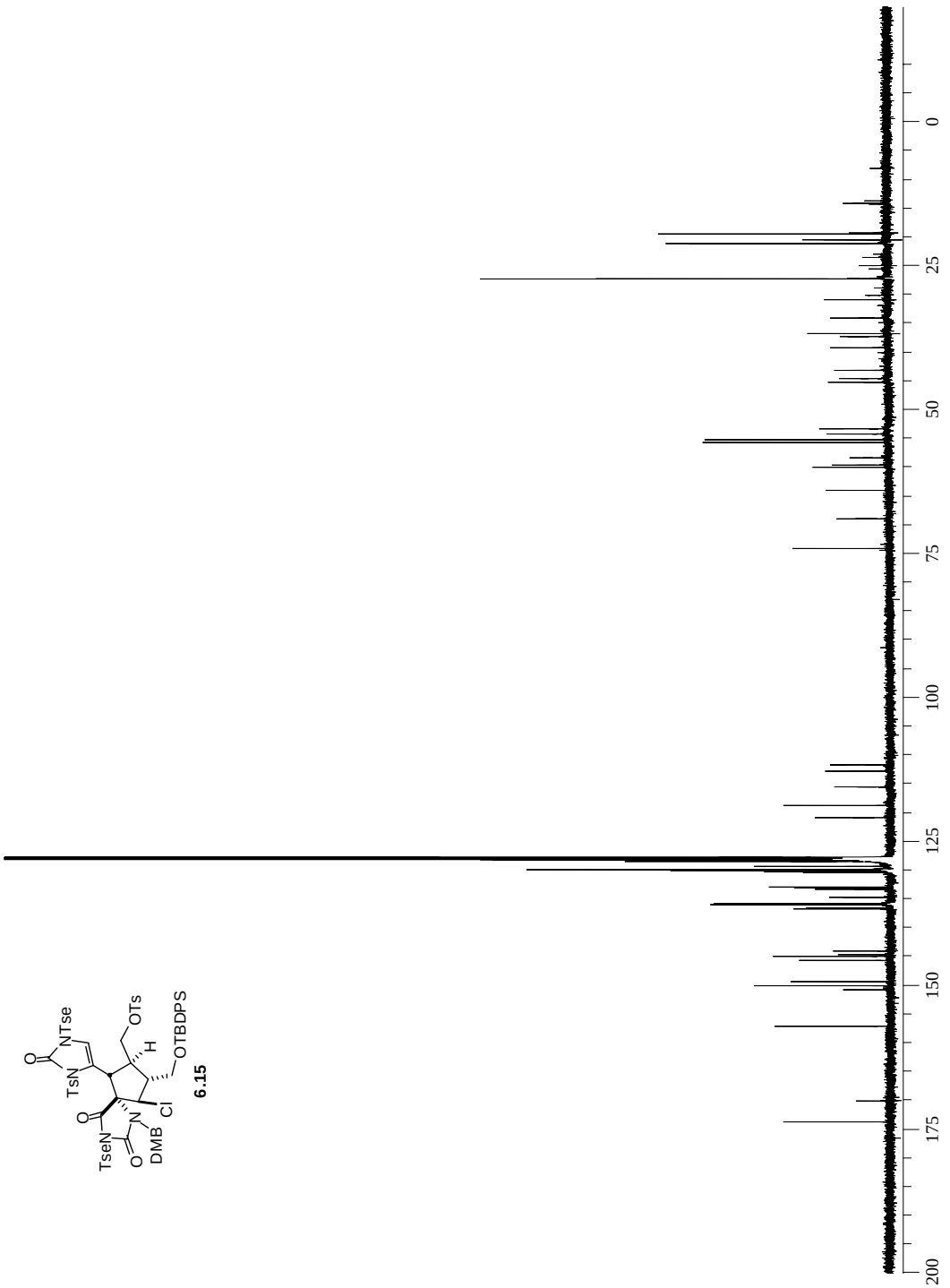
^{13}C-NMR spectrum of alcohol **6.14** (in benzene-d_6)



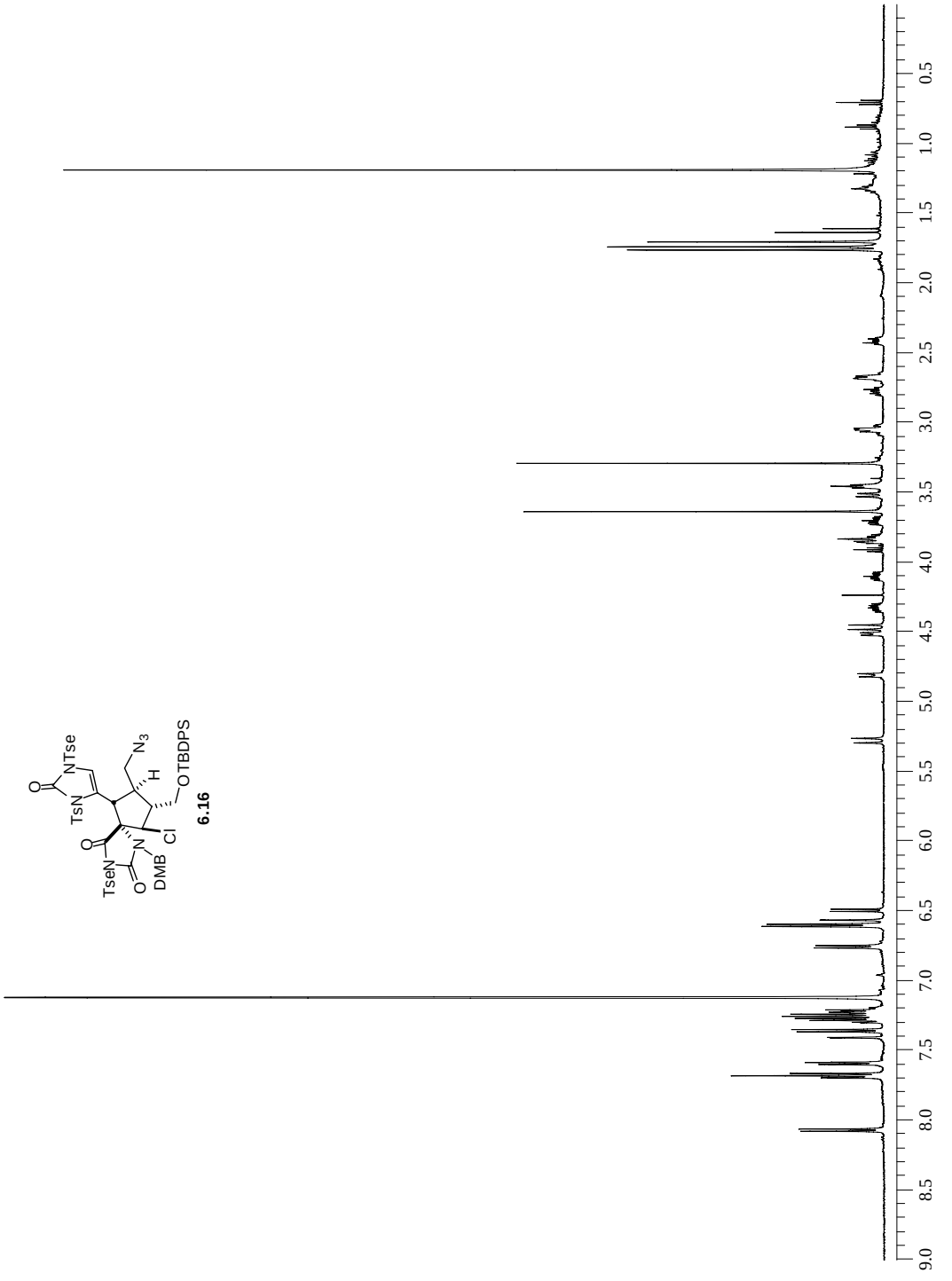
6.15



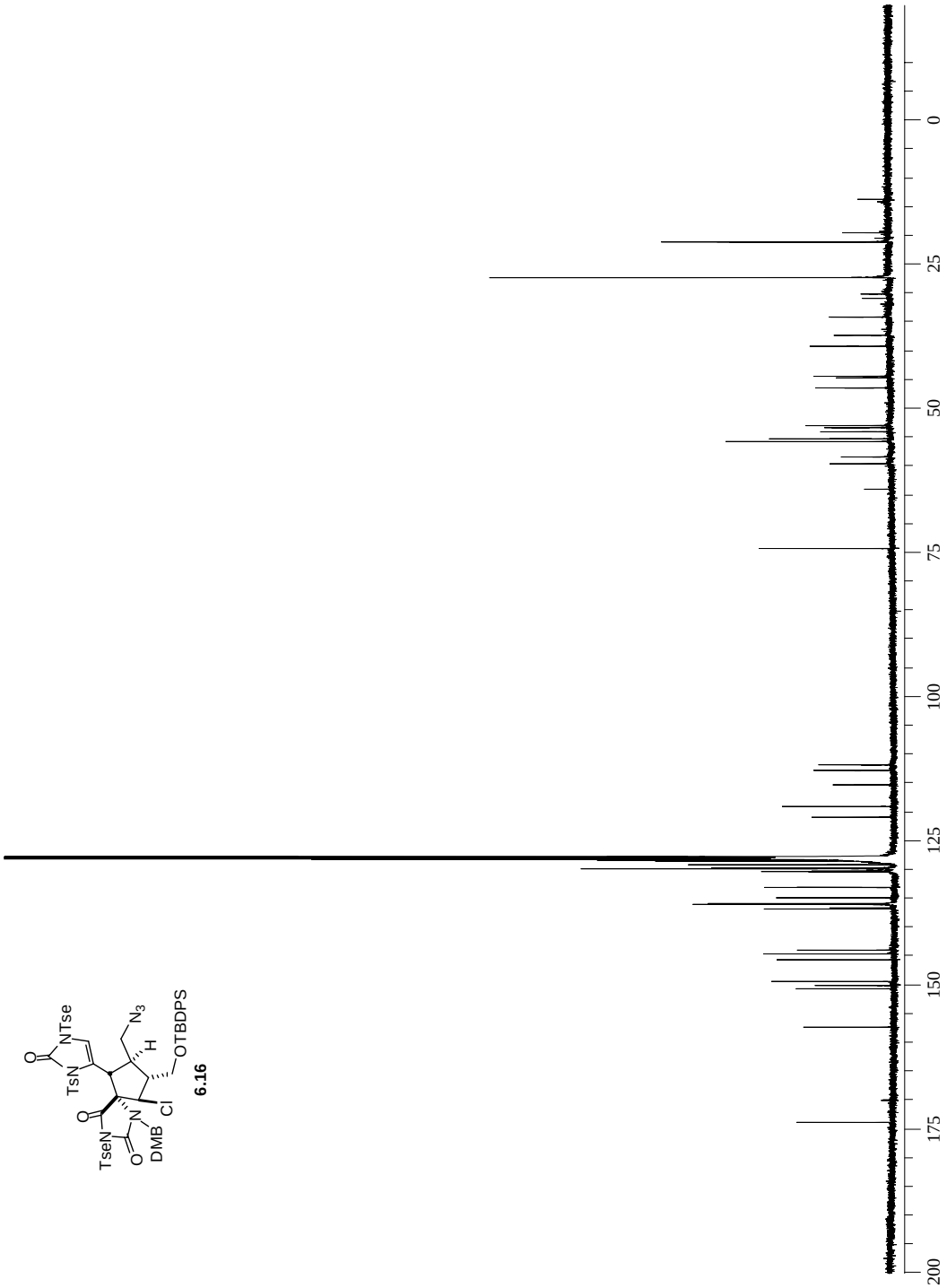
^{1}H-NMR spectrum of tosylate **6.15** (in benzene-d_6)



^{13}C-NMR spectrum of tosylate **6.15** (in benzene-d_6)



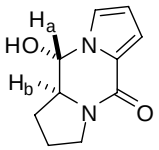
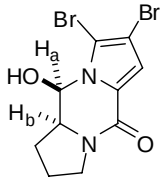
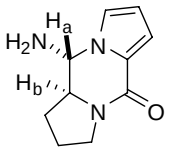
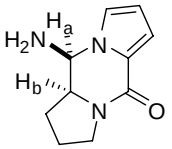
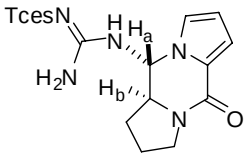
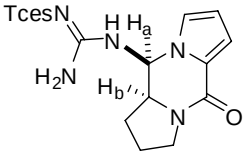
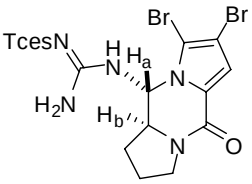
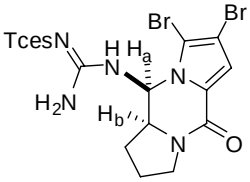
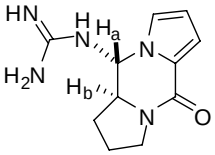
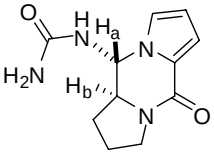
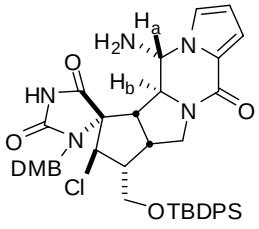
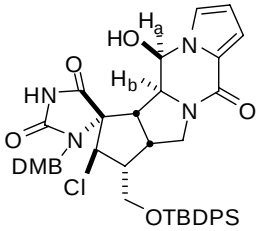
^{1}H-NMR spectrum of azide **6.16** (in benzene-d_6)



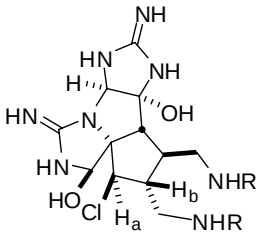
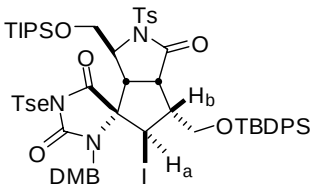
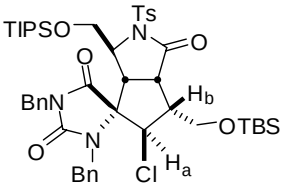
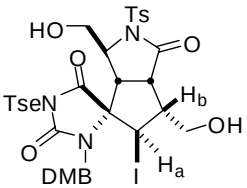
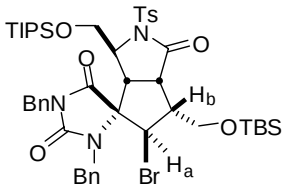
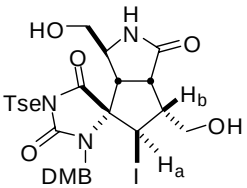
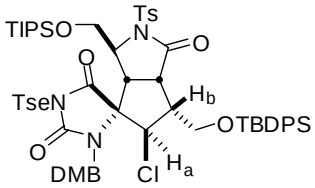
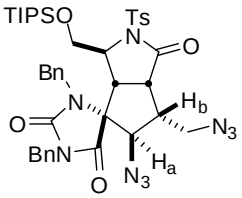
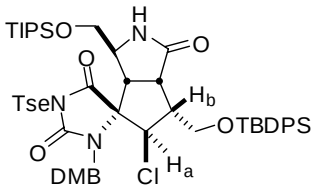
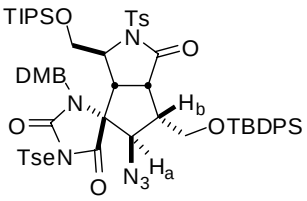
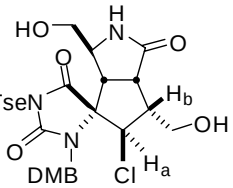
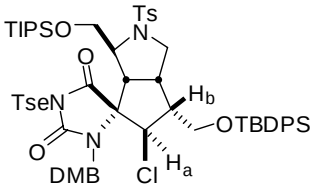
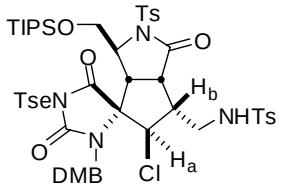
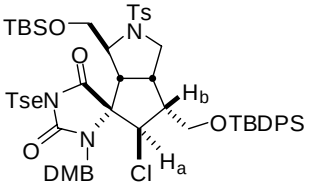
^{13}C-NMR spectrum of azide **6.16** (in benzene-d_6)

APPENDIX B

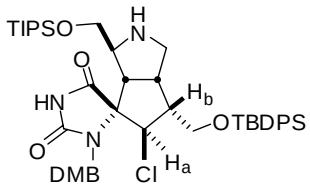
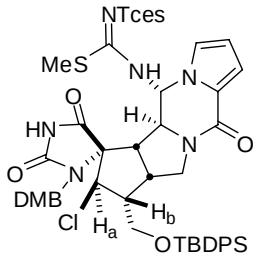
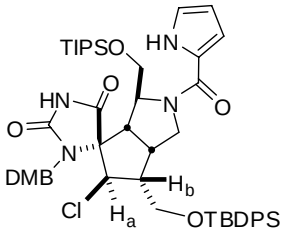
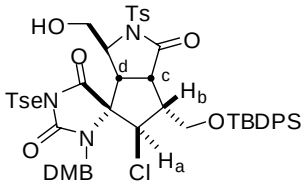
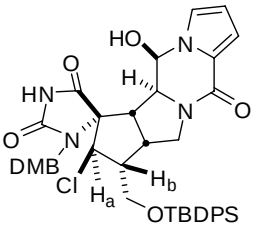
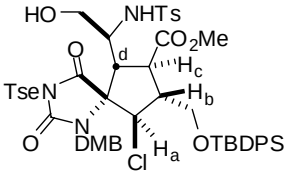
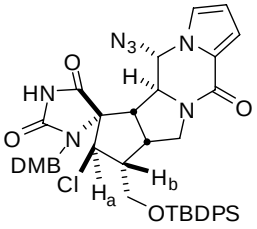
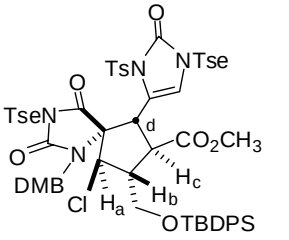
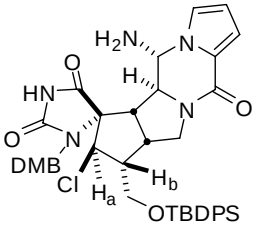
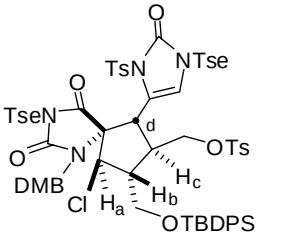
COUPLING CONSTANT COMPARISONS

structures	coupling constants	structures	coupling constants
	J_{ab} = 9.7 Hz *		J_{ab} = 2.6 Hz *
	J_{ab} = 10.0 Hz		J_{ab} = 3.0 Hz
	J_{ab} not observed structure confirmed by X-ray analysis		J_{ab} = 2.5 Hz
	J_{ab} = 10.0 Hz		J_{ab} not observed structure confirmed by X-ray analysis **
	J_{ab} = 10.5 Hz		
	J_{ab} = 10.5 Hz		
	J_{ab} = 10.0 Hz		J_{ab} = 3.0 Hz

*: Lindel and co-workers: *Tetrahedron Lett.* **2002**, *43*, 3699-3702.
: Francisco M. Franco-Torres, M.S. thesis, Texas A&M University, **2007.

structures	coupling constants	structures	coupling constants
	J_{ab} = 12.0 Hz *		J_{ab} = 13.5 Hz
	J_{ab} = 12.5 Hz **		J_{ab} = 13.0 Hz
	J_{ab} = 12.9 Hz **		J_{ab} = 12.5 Hz
	J_{ab} = 12.5 Hz		J_{ab} = 11.1 Hz **
	J_{ab} = 11.0 Hz		J_{ab} = 11.0 Hz
	J_{ab} = 12.0 Hz		J_{ab} = 12.0 Hz
	J_{ab} = 11.5 Hz		J_{ab} = 11.5 Hz

*: Quinn and co-workers: *J. Org. Chem.* **1999**, *64*, 731-735.
: Anja S. Dilley, Ph.D. dissertation, Texas A&M University, **2003.

structures	coupling constants	structures	coupling constants
	J_{ab} = 12.0 Hz		J_{ab} = 12.0 Hz
	J_{ab} = 12.0 Hz		J_{ab} = 12.5 Hz J_{bc} = 8.0 Hz J_{cd} = 8.5 Hz *
	J_{ab} = 12.0 Hz		J_{ab} = 11.5 Hz J_{bc} = 11.5-12.0 Hz J_{cd} = 11.5-12.0 Hz *
	J_{ab} = 12.5 Hz		J_{ab} = 11.5-12.0 Hz J_{bc} = 11.0-11.5 Hz J_{cd} = 11.0 Hz *
	J_{ab} = 12.5 Hz		J_{ab} = 11.5 Hz J_{bc} not observed J_{cd} = 10.0 Hz *

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